Alkylboronic Esters as Radical Precursors: Applications to Deboronative Radical Chain Reactions

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Der Dekan:
Prof. Dr. Zoltan Balogh

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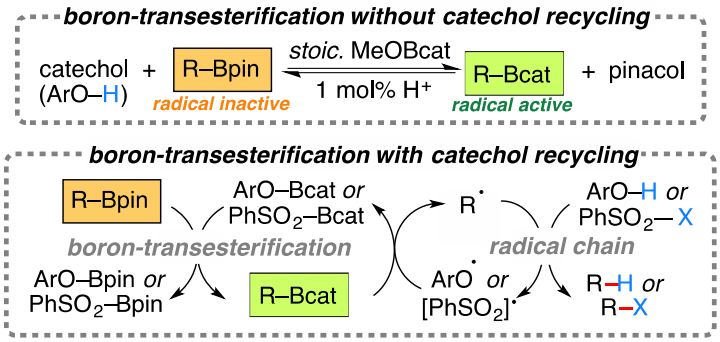
Abstract

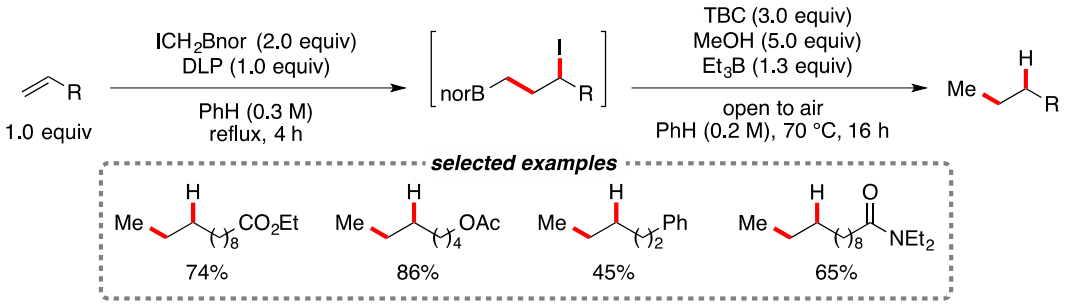
Many efforts have been made in developing valuable transformations taking advantage of the electron deficiency caused by the vacant p-orbital of boron and the metallic properties of its derivatives. Organoboron derivatives have proven over the years to be a versatile source of alkyl radicals. The generation of carbon-centered radicals from air-sensitive *B*-alkylcatecholborane through nucleohomolytic substitution at boron is well-established and became a general method to generate alkyl radicals. The high reactivity of catechol alkylboronic esters towards heteroatom-centered radical (e.g. O_2) causes stability issues for purification processes and long-term storages. However, the generation of radicals from bench-stable boronic esters such as pinacol alkylboronic esters is not suitable due to their reduced Lewis acidity and lack of radical resonance-stabilization.

Our studies focused on an *in situ* conversion of pinacol alkylboronic esters into catechol alkylboronic esters, achievable by boron-transesterification. This transformation was tailored to various radical chain deboronative processes enabling C—X, C—S, C—C and C—H bonds formation (Scheme 1).



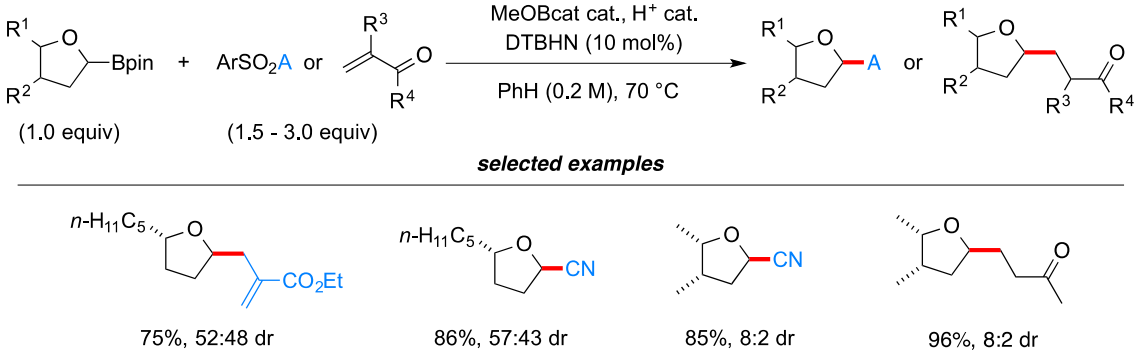
Scheme 1. Deboronative radical chain reactions with pinacol alkylboronic esters

Besides, we investigated the *in situ* boron-transesterification using further bench-stable boronic ester precursors, i.e., norbornanediol boronic esters. Ultimately, we applied this chemistry to the underdeveloped anti-Markovnikov hydromethylation of unactivated alkenes by merging an iodine atom transfer radical addition (I-ATRA) of norbornanediol iodomethyl boronate (ICH_2Bnor) onto unactivated alkenes, and the previously exploited protodeboronative radical chain process (Scheme 2).

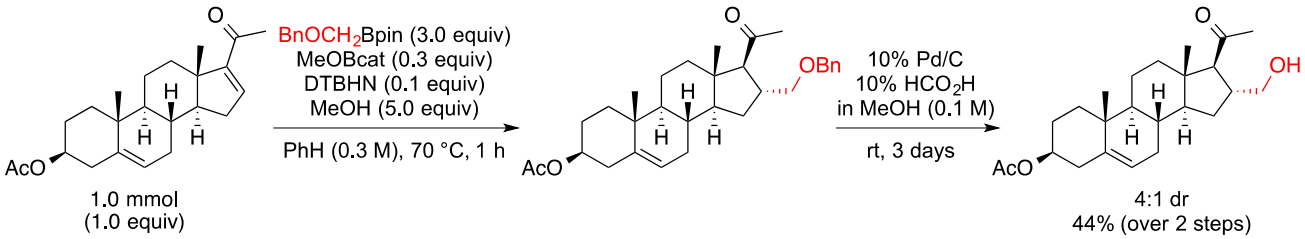


Scheme 2. Anti-Markovnikov hydromethylation of unactivated alkenes

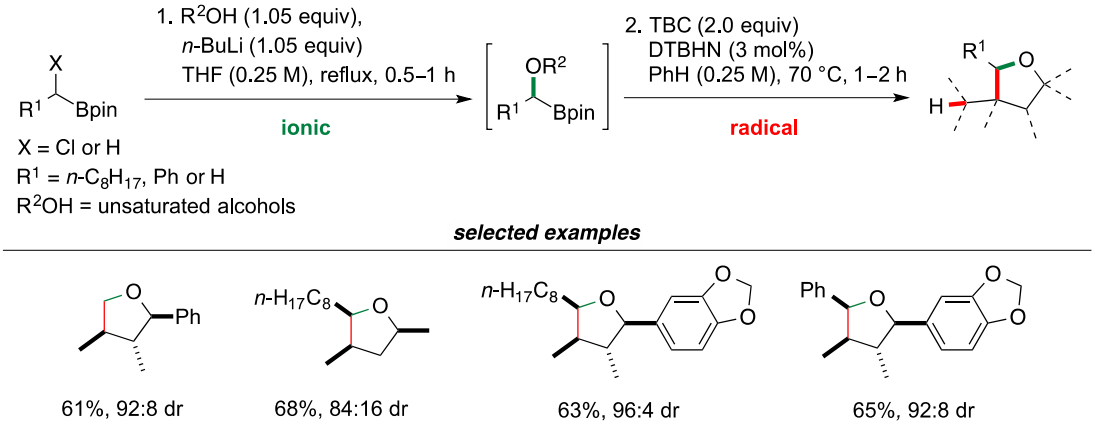
Additionally, the generation of cyclic and acyclic 1-alkoxyalkyl radicals was explored using our deboronative approach from pinacol alkoxyalkylboronic esters. The synthetic utility of our method was thoroughly studied, allowing the synthesis of 2-alkylated tetrahydrofurans (THF) and tetrahydropyrans (THP) using various radical chain deboronative processes (Scheme 3), the hydroalkoxymethylation of Michael acceptors (Scheme 4), and the construction of substituted-THF ring systems through radical cyclization (Scheme 5).



Scheme 3. Preparation of 2-alkylated THF rings



Scheme 4. Hydroalkoxymethylation of Michael acceptors



Scheme 5. Construction of THF ring systems via intramolecular cyclization

List of Abbreviations

$[\alpha]_D^{20}$	Specific rotation at 20 °C
δ	Chemical shift (in ppm)
AIBN	2,2'-Azobis(isobutyronitrile)
aq.	Aqueous
Ar	Aromatic or Argon
Atm	Atmosphere
ATRA	Atom Transfer Radical Addition
BDE	Bond Dissociation Energy
Bcat	Catechol boronic ester
Bpin	Pinacol boronic ester
cat.	Catalytic
calcd.	Calculated
conc.	Concentrated
DCE	1,2-Dichloroethane
DHP	Dihydropyridine
DLP	Dilauroyl peroxide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	Ethylenebis(diphenylphosphine)
dppm	Methylenebis(diphenylphosphine)
DTBHN	Di-tert-butyl hyponitrite
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
dr	Diastereosimeric ratio
E^+	Electrophile
EDG	Electron donating group
EI	Electronic Ionization
equiv	Equivalent
ESI	Electron spray ionization
EWG	Electron withdrawing group
FCC	Flash column chromatography

FID	Free induction decay
GC	Gas Chromatography
h	Hour
H^+	Acid
hν	Light irradiation
HAT	Hydrogen Atom Transfer
HRMS	High Resolution Mass Spectroscopy
IR	Infrared spectroscopy
J	Coupling constant (in Hz)
LA	Lewis acid
LDA	Lithium diisopropyl amide
m/z	Mass to charge ratio
MOM	Methoxymethyl ether
m.p.	Melting point
MS	Mass spectroscopy
NIS	N-iodosuccinimide
NMR	Nuclear Magnetic Resonnance
nOe	Nuclear Overhauser Effect
Nu^-	Nucleophile
PET	Photoinduced electron transfer
PhH	Benzene
PMB	*p*-Methoxybenzyl
ppm	Parts per million
RATC	Radical-Addition-Translocation-Cyclization
rt	Room temperature
RT	Retention time
TAG	Traceless activation group
TBC	4-*tert*-Butylcatechol
TBDMS	*tert*-Butyl dimethyl silyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl ether
THF	Tetrahydrofuran

THP	Tetrahydropyran
TLC	Thin layer chromatography
Tol	*p*-Toluene
TTMSS	Tris-(trimethylsilyl)silane
sat.	Saturated
SCE	Saturated calomel electrode
SET	Single electron transfer
S_H2	Second order homolytic substitution
UV	Ultra-violet

Contents

1

Organoboron Derivatives as a Source of Radicals

Accepted in:

André-Joyaux, E.; Gnägi, L.; Gnägi-Lux, M.; Melendez Becerra C. A.; Soulard V.; Tappin, N. D. C.; Renaud, P.

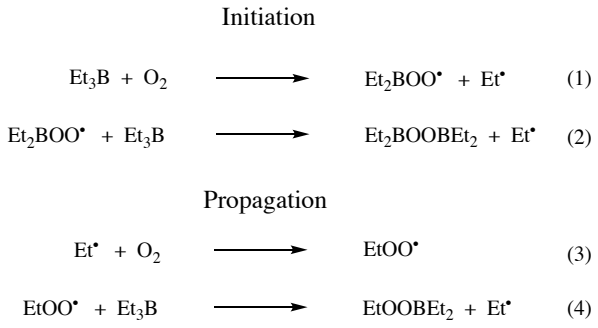
Boron Mediated Radical Reactions,

Patai's Chemistry of Functional Groups **2020**

1. Organoboron derivatives as a source of radicals

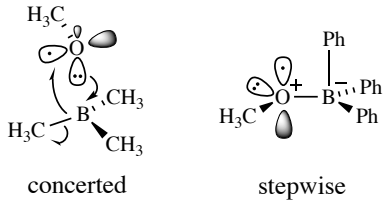
1.1 Basics principles

The system organoborane/air is widely used to initiate radical chain reactions.[1–3] Its success is mainly due to the simplicity of the process since the reaction requires neither heating nor irradiation and can be conducted at any temperature by simple addition of a controlled amount of air to reactions mixtures containing a trialkylborane. Interestingly, organoboranes are rather stable an unreactive species except for their reaction with oxygen that occurs even at low temperature.[4] The mechanism of the autoxidation has been intensively investigated.[4–6] The first step of the initiation process is the reaction of triethylborane with oxygen that gives a boroperoxyl radical and an ethyl radical that can enter the propagation step (Scheme 1, eq. 1). This spin forbidden reaction is a slow process with an estimated rate constant of 7×10^{-4} M^{-1} s^{-1}.[7] However, despite its relative slowness, this reaction is working even at low temperature and the boroperoxyl formed in step 1 (Scheme 1, eq. 1) reacts very rapidly with triethylborane to furnish a second ethyl radical (Scheme 1, eq. 2) that can propagate a second chain process. The two propagation steps (Scheme 1, eq. 3 and 4) are very fast, therefore, the autoxidation of triethylborane can be considered as a very efficient chain reaction whose initiation is slow.[8]



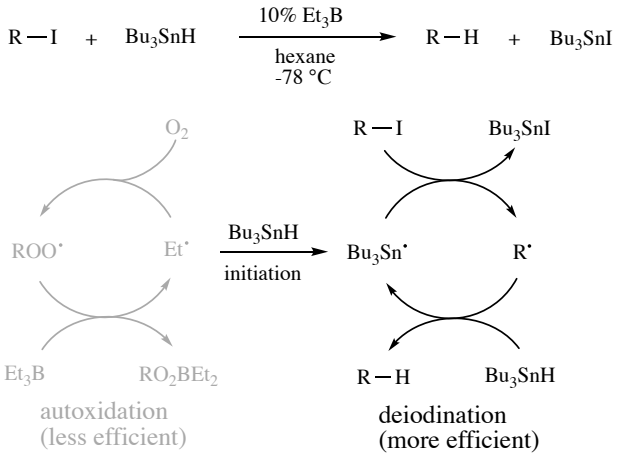
Scheme 1. Simplified mechanism for the autoxidation of triethylborane

From a mechanistic point of view, the reaction of oxygen-centered radical with trialkyl- and triarylboranes corresponds to nucleohomolytic substitution where the oxygen lone pair of electron is interacting with empty p-orbital at boron and the mono-occupied orbital at oxygen is involved in a β-fragmentation process (Scheme 2). A concerted mechanism is operating for trimethylborane and a stepwise process involving the formation of an intermediate ate complex is taking place for triphenylborane.[9]



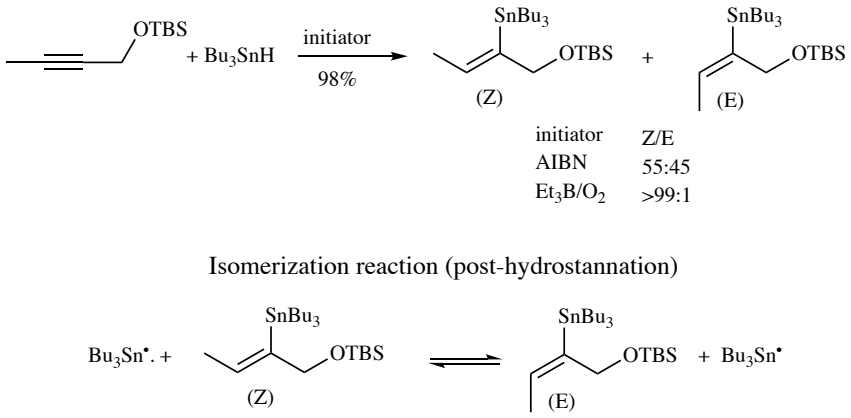
Scheme 2. Reactivity of heteroatom-centered radicals towards organoboranes

Recently, the mechanism of the initiation of radical chain reactions with triethylborane has been carefully investigated by Curran and McFadden.[8] They are highlighting the difference between AIBN and Et_3B/O_2 initiation systems. Both reagents are providing radicals that can enter most chain processes, AIBN via a monomolecular process, Et_3B via a bimolecular reaction with O_2 and both initiating agents are most of the time fully interchangeable. However, the presence of O_2 in the Et_3B initiation process has some consequences that may lead to unexpected results and less efficient initiation. Curran and McFadden propose to differentiate between low- and high-oxygen regimes.[8] Small amount of triethylborane and traces of oxygen characterize the low-oxygen regime. This type of initiation is suitable for efficient chain processes where the slowest step of the target chain reaction is faster than the rates of all the competitive radical reactions with O_2. Curran illustrated this regime with the tin hydride reductive deiodinations developed by Utimoto and Oshima (Scheme 3). In this specific example, the concentration of O_2 is 500 times lower than tin hydride and is consumed by autoxidation chain. Under such conditions, ethyl radicals react with tin hydride rather than O_2 providing an efficient initiation of the chain deiodination process. The competing autoxidation process (Scheme 3, grey part) is a minor side reaction.



Scheme 3. Et_3B initiated deiodination reaction

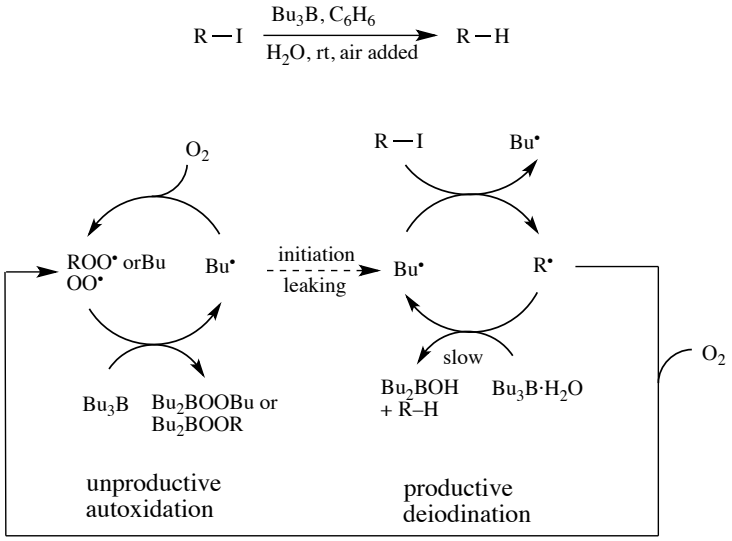
Curran and McFaden have demonstrated, that counterintuitively AIBN may be a more efficient radical initiator than Et_3B when the chain reaction involves single steps that are not very fast. This point is convincedly demonstrated by their study of the mechanism of the hydrostannation of propargyl alcohols reported initially by Organ and coworkers.[10] The two initiators work equally well in term of yield but provide the hydrostannylated with a different stereochemistry (Scheme 4). AIBN, the best initiator, provides a nearly 1:1 mixture of *Z/E* stereoisomers while Et_3B/O_2 afford the *Z*-isomer with a good stereoselectivity. This result is explained by the fact that both initiators are able to initiate efficiently the hydrostannation process (leading to the *Z*-isomer under kinetic control) but that only AIBN is able to initiate the slower tin radical mediated isomerization process affording a *Z/E* mixture of products (thermodynamic control).



Scheme 4. Hydrostannation of propargyl alcohol: AIBN vs. Et_3B/O_2 (low-oxygen regime).

When the targeted chain reactions involve slower step, the autoxidation competes efficiently with the desired chain reaction. In such cases, the high-oxygen regime may be used to achieve effective transformation. Under this regime, large amounts of Et_3B (0.5–3 equiv) and periodic or continuous addition of air is used. Indeed, if the rate of the slowest step of the productive chain is less efficient than autoxidation, autoxidation can consume all the initiator in its propagation steps. This process describes the high-oxygen regime. This type of initiation is illustrated by the $Bu_3B{\cdot}H_2O$ complex-mediated reductive deiodination developed by Wood and coworkers (Scheme 5).[11] Since the rate of the H-transfer step is slow ($k_H = 4 \times 10^4$ M^{-1} s^{-1}), alkyl radicals can in a competitive pathway with oxygen provide a peroxyl radical that trigger the autoxidation process. This unproductive oxidation of the alkyl radical results automatically in a decreased yield of the target product. However, by adjusting the concentration of oxygen,

efficient reaction can be performed. The initiation of the productive deiodination reaction takes place via leaking of the butyl radicals from the autoxidation process to the production chain reaction. The high-oxygen regime requires fine tuning of the reaction conditions and consumes moderate to large amount of Et_3B and O_2 but it can lead to efficient preparative transformations.

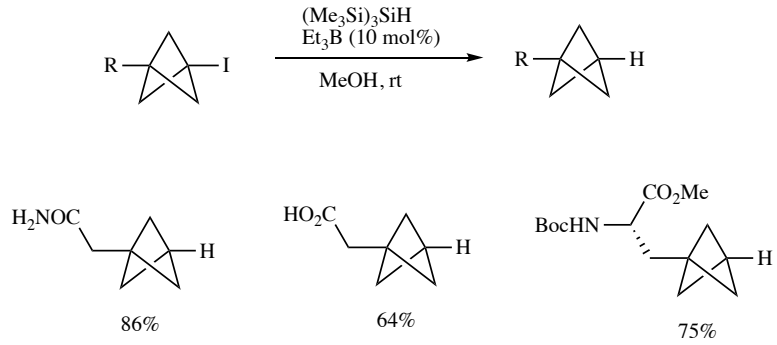


Scheme 5. High-oxygen regime in reductive deiodination

1.2 Initiation of chain reactions

1.2.1 Et_3B as an initiator for simple dehalogenation process

Et_3B has been used as an initiator for a broad range of tin hydride and silane mediated dehalogenation processes and this chemistry has been extensively reviewed in the past.[3,12] This method is very general but particularly recommended for low temperature initiation. This chemistry has been recently used by Anderson and coworkers for the deiodination of iodobicyclo[1.1.1]pentane derivatives using tris(trimethylsilyl)silane as a source of hydrogen atom (Scheme 6).[13]

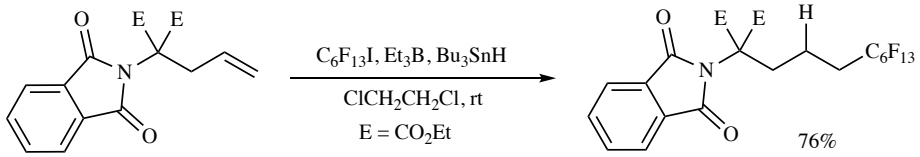


Scheme 6. Deiodination of iodobicyclo[1.1.1]pentane derivatives

Hydrogen atom abstraction from water–Et_3B complex was discovered by Wood and co-workers for the radical reduction of xanthates.[14] This discovery represents a very attractive method to overcome the use of toxic metal hydrides (discussed in another section of the Patai).

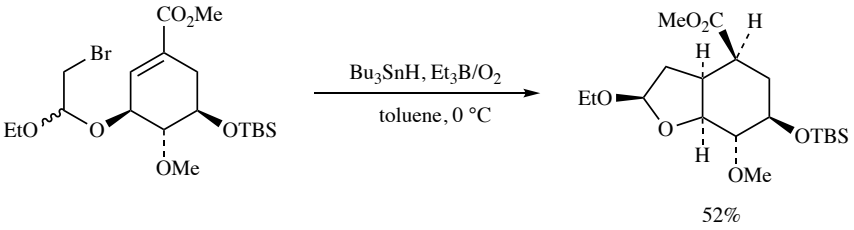
1.2.2 Et_3B as an initiator for C–C bond formation in the presence of a hydrogen atom donor

Perfluoroalkylation of α-amino acids followed by *in situ* deiodination was achieved using Et_3B/O_2 initiator system and *n*-Bu_3SnH as a reducing and chain carrier reagent (Scheme 7).[15] The process proved to be efficient at room temperature using only 15 mol% of Et_3B.



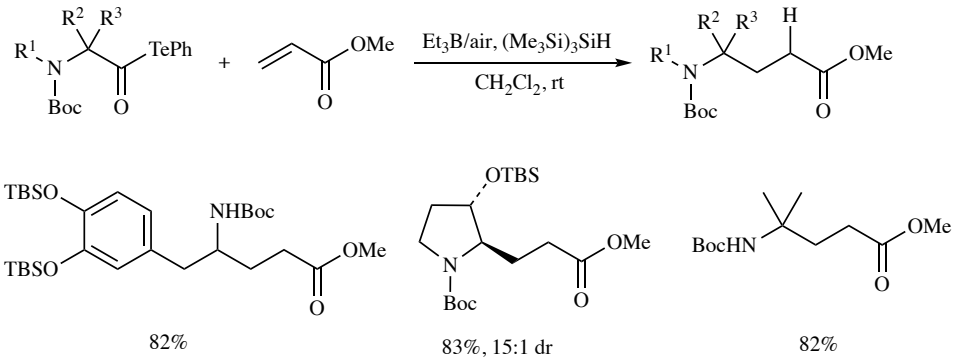
Scheme 7. Perfluoroalkylation of α-amino acids

Radical cyclization initiated by Et_3B/O_2 has become a standard procedure. Huang and Chen used this procedure for the intramolecular radical cyclization of the α-bromo acetal to build the potential E-ring segment of the indole alkaloids (–)-reserpine.[16] Treatment with Et_3B/*n*-Bu_3SnH at 0 °C yielded the cyclized compound with the desired (*S,S*)-configuration (Scheme 8).



Scheme 8. Potential E-ring segment of the indole alkaloids (-)-reserpine

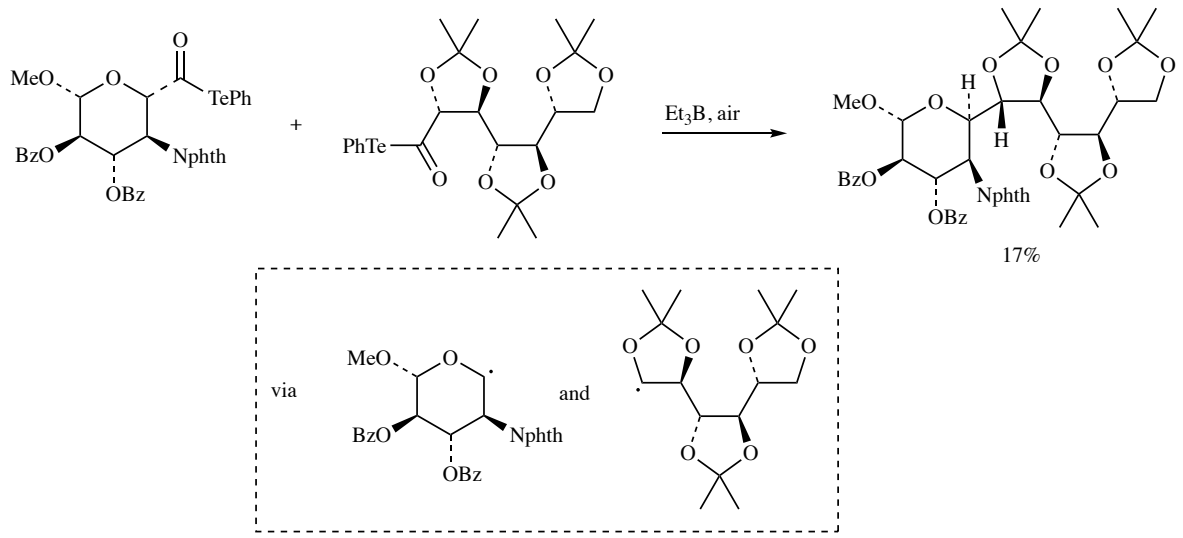
The system Et_3B/air has also been used to initiate reactions involving silanes and germanes as hydrogen atom donors. For instance, Inoue and coworkers reported a decarbonylative radical coupling of α-aminoacyl telluride using trimethylsilane upon initiation with Et_3B and O_2 at room temperature (Scheme 9).[17]



Scheme 9. Decarbonylative radical coupling of α-aminoacyl telluride

1.2.3 Initiation of radical dimerization

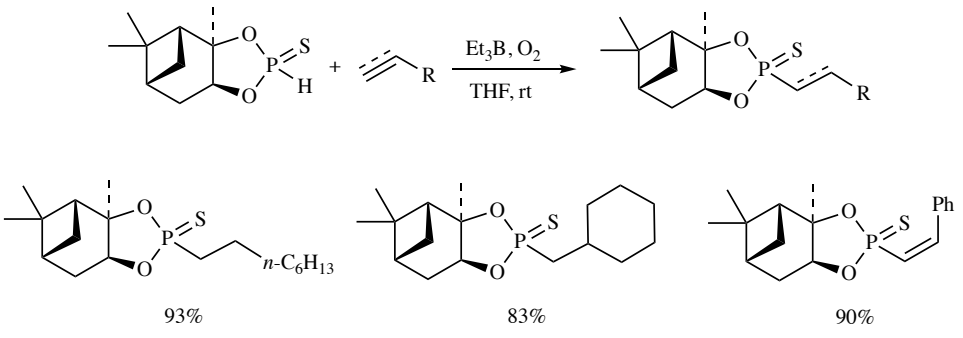
Inoue and co-workers reported an efficient approach for the decarbonylative dimerization of acyl tellurides. In this process, the radicals were generated using a stoichiometric amount of Et_3B.[18] This non-chain process proved to be efficient with a broad range of highly oxygenated systems leading to surprisingly efficient homo- and even heterocoupling products (Scheme 10).



Scheme 10. Decarbonylative heterocoupling of α-oxygenated radicals

1.2.4 Et_3B as an initiator for C–X bond formation in the presence of a hydrogen atom donor

The addition of tris(trimethylsilyl)silane,[19,20] thiols,[21] germanes,[22–24] gallium hydride[25] and phosphorus based reagents[26] to alkenes and/or alkynes can be easily conducted in the presence of Et_3B/O_2. After Piettre and co-workers showed that thiophosphites can add more efficiently to alkenes than phosphites, Parsons and coworkers reported the addition of chiral thiophosphites to alkenes and alkynes with retention of the configuration at the P-center (Scheme 11).[27] Epimerization of the thiophosphite was observed upon heating dismissing the use of peroxide initiators and AIBN for this reaction.

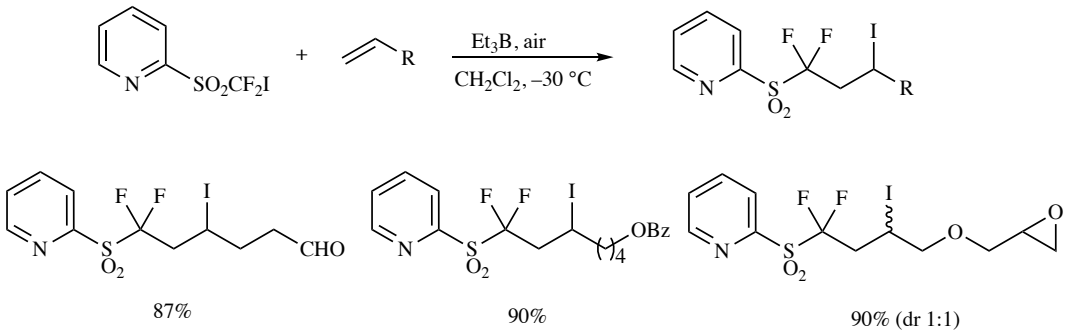


Scheme 11. Addition of achiral thiophosphites to alkenes and alkynes

Oshima and coworkers developed an efficient triethylborane initiated hydrothiolation of alkynes.[21] Renaud, Bonnaffé, and coworkers reported a unique repair mechanism for thiol-ene coupling reactions involving allylic ether and *O*-benzylated alkenols (this reaction is discussed in another section of the Patai).[28]

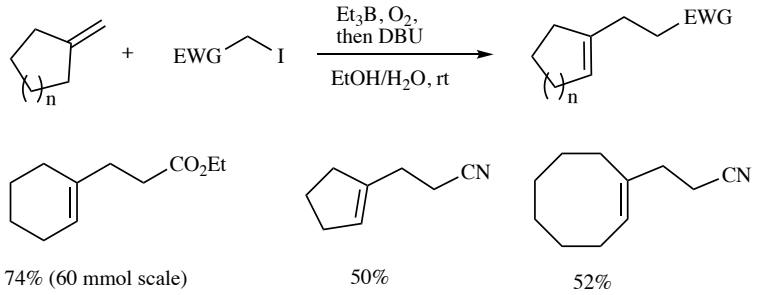
1.2.5 Et_3B in atom transfer and related reactions

Oshima and coworkers have demonstrated that the system Et_3B/O_2 is particularly suitable for bromine[29] and iodine atom transfer reactions.[30] The capacity of Et_3B to act as an initiator in water has been demonstrated with success in the atom transfer radical addition and cyclization of halogenated compounds.[31,32] Many Et_3B-induced intermolecular radical addition of iodine precursors to alkenes and alkynes have been reported.[33,15] Hu and coworkers developed a (2-pyridylsulfonyl)difluoromethylation of terminal alkenes using Et_3B in an open to air reaction vessel (Scheme 12).[34] Best yields were obtained by using a substoichiometric amount of Et_3B and by carrying the reaction at low temperature.



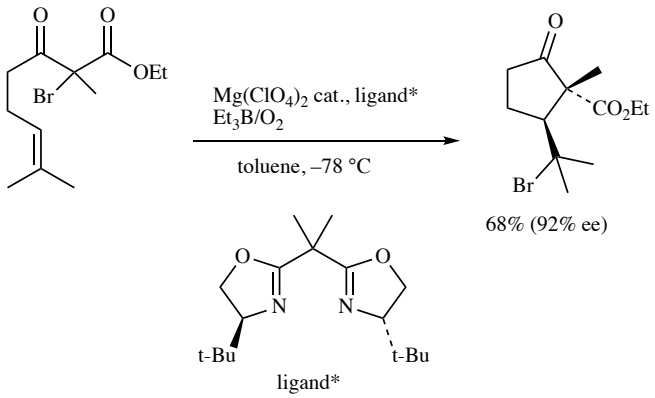
Scheme 12. Radical (2-pyridylsulfonyl)difluoromethylation of terminal alkenes

Recently, the preparation of functionalized 1-substituted cycloalkenes involving an iodine ATRA followed by an *in situ* base promoted elimination was reported (Scheme 13).[35] Best results were obtained in a mixture of water/ethanol as solvent. The reaction was performed up to a 60 mmol scale.



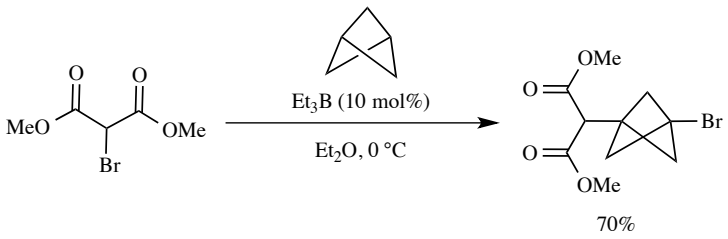
Scheme 13. Iodine ATRA-elimination process for the preparation of functionalized 1-substituted cycloalkenes

Et_3B-initiated radical cascade reactions with 1,6-dienes and 1,6-enynes have been applied to the synthesis of chiral γ-lactams.[36,37] High diastereoselectivities were reached by running the reactions at low temperature with a combination of hydroxamate esters and chiral Lewis acids. Et_3B-induced radical cascade reactions with 1,5-enynes and 1,5-diynes were also applied to the synthesis of dioxatriquinanes and tricyclic glucoconjugates.[38,39] Enantioselective cascade processes involving a bromine atom transfer at –78 °C under Et_3B/O_2 initiation system were reported by Yang and coworkers using a catalytic amount of chiral Lewis acid for the synthesis of cyclic 2,3-disubstituted ketones (Scheme 14).[40] Porter and coworkers showed that intermolecular atom-transfer radical addition reactions were strongly facilitated by Lewis acids such as $Sc(OTf)_3$ or $Yb(OTf)_3$.[41] The transfer of phenylselanyl group initiated by the system Et_3B/O_2 works very efficiently in the presence of Lewis acids and promising enantioselectivities have been reported by Yang.[42]



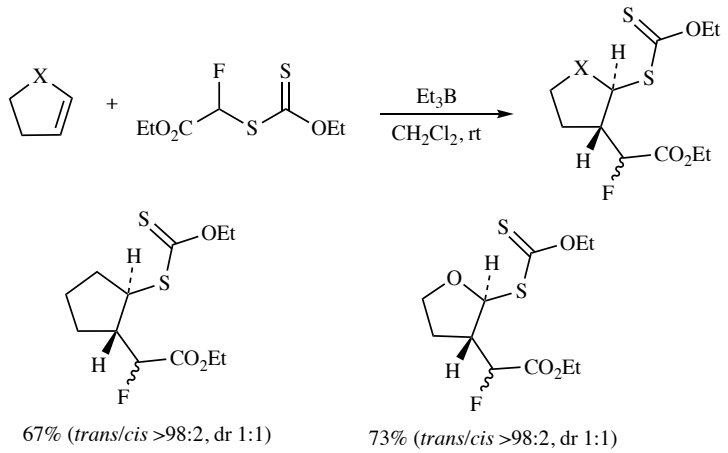
Scheme 14. Low temperature enantioselective cyclization initiated by Et_3B

Intermolecular bromine and iodine ATRA reactions mediated by Et_3B were used by Anderson and coworkers for the synthesis of functionalized bicyclo[1.1.1]pentanes (Scheme 15).[13]



Scheme 15. Synthesis of 1-halo-3-substituted bicyclo[1.1.1]pentanes

The transfer of xanthates is a powerful method for C–C bond formation developed by Zard.[43,44] Initiation is usually performed with peroxides such as lauroyl peroxide at temperatures above 80 °C. Lequeux and coworkers reported the transfer of xanthate to dihydrofuran and cyclopentene in the presence of lauroyl peroxide in refluxing DCE.[45] However, the difficulty to remove the lauroyl peroxide brought them to use Et_3B as an alternative initiator (Scheme 16).



Scheme 16. Et_3B mediated addition of xanthates to alkenes

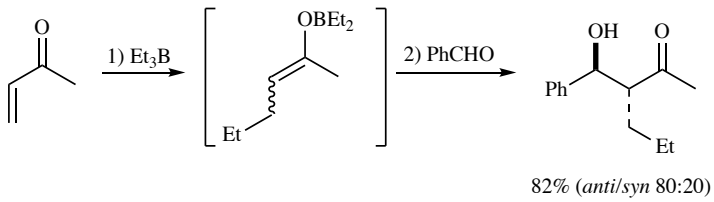
The use of Et_3B at lower reaction temperature was also used to increase the diastereoselectivity of the radical addition of xanthate to allylsilane.[46] Xanthate transfer reactions were performed as well in aqueous media using Et_3B/O_2 initiation system.[47]

1.3 Reaction involving boron based radical precursor

1.3.1 Chain reaction with trialkylboranes

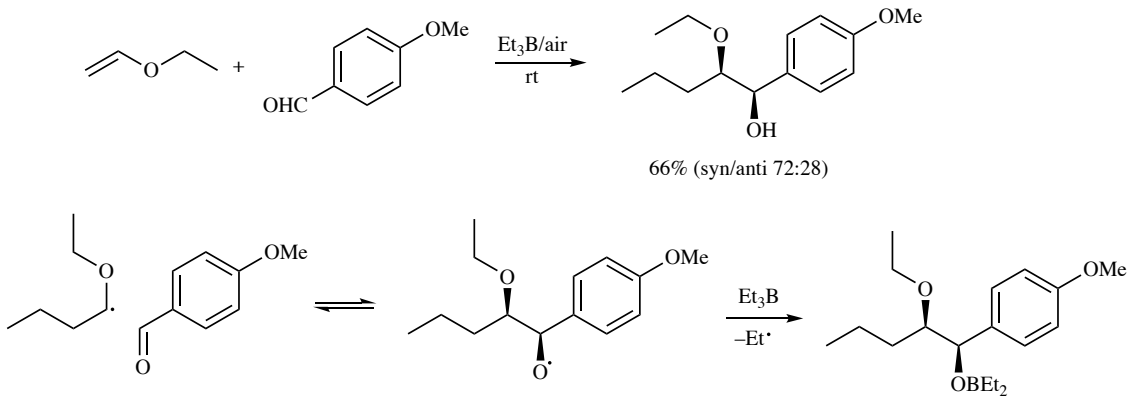
1,2-Addition of radicals generated from trialkylboranes to imines and related compounds has been reviewed.[48] The control of the chemistry using chiral auxiliary approaches was investigated. For instance, Somfai and coworkers extended the method to chiral ester of 2*H*-azirine-3-carboxylate under Lewis acid activation, with CuCl to prepare optically active α-alkylated aziridine-2-carboxylates.[49] Addition of ethyl radicals to aldimines affords the addition products in fair to good yields but with low diastereocontrols.[50] Similar reactions with aldoxime ethers, aldehyde hydrazones, N-sulfonylaldimines and ketimines are reported.[51–54]

Alkyl radicals generated from trialkylboranes undergo 1,4-addition to enones and enals. This reaction has been well established by Brown and coworkers and represent one of the first synthetic application of organoboranes in radical chemistry.[55–58] Initiation with oxygen, diacetyl peroxide, or irradiation is however necessary for the addition to β-substituted enones and enals.[59,60] Brown proposed a mechanism where the enolate radical formed reacts with the trialkylborane to give a boron enolate and a new alkyl radical that can propagate the chain. This mechanism was further confirmed by Mukayiama and coworkers with the characterization of the intermediate boron enolate by ^{1}H NMR spectroscopy.[61] The latter is rapidly hydrolyzed by water present in the system to prevent side reactions. Several attempts to trap the intermediate boron enolate to achieve tandem conjugate addition–aldol reaction were reported[62] as illustrated by the Et_3B conjugate addition–aldol reaction developed by Chandrasekhar and coworkers for the synthesis of α-alkyl-β-hydroxy ketones (Scheme 17).[63]



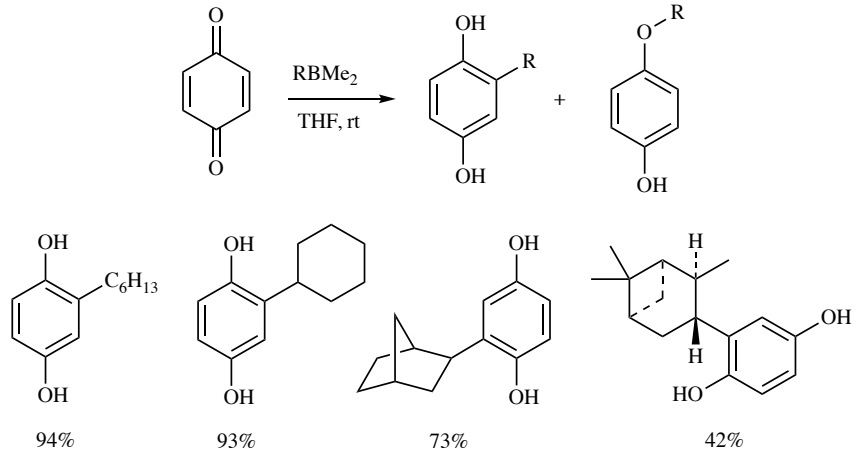
Scheme 17. Radical mediated generation of boron enolates and their trapping with aldehydes

A radical hydroxyalkylation of ethyl vinyl ether initiated by the system Et_3B/air has been described (Scheme 18).[64] The reaction involves the addition of an ethyl radical to the vinyl ether followed by trapping of the transient radical with 4-methoxybenzaldehyde.



Scheme 18. Radical hydroxyalkylation of ethyl vinyl ether

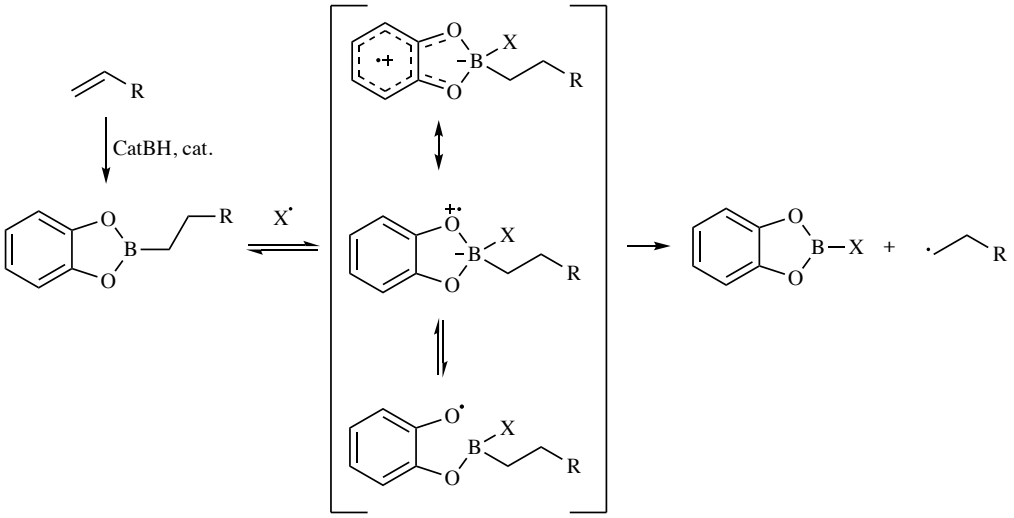
Addition of Et_3B to activated olefins such as ylidene malonitrile proved to be efficient at room temperature and under air atmosphere in an Et_2O/H_2O biphasic medium.[65] The main issue of this approach is that only one out of the three alkyl groups of trialkylborane is transferred, limiting this method to the use of trialkylboranes obtained by hydroboration of easily available and cheap alkenes. A restricted solution to this problem was proposed with *B*-alkylboracyclanes,[66,67] which is not appropriate for primary alkyl radicals and for radical traps substituted at the β-position. Similar chemoselectivity issues were observed when attempting to use cyclohexyldiethylborane to generate cyclohexyl radicals.[68] More recently, the use of alkyldiphenylborane and alkyldimethylborane was reported for addition to benzoquinone. In this case, the lack of selectivity in the cleavage of trialkylboranes was minimized, giving good yield for the *C*-alkylation of primary and secondary groups (Scheme 19).[69] In this reaction, tertiary and secondary groups with steric bulk gave *O*-alkylation as the major product.[70]



Scheme 19. Radical addition to benzoquinones

1.3.2 Chain reactions with *B*-Alkylcatecholboranes

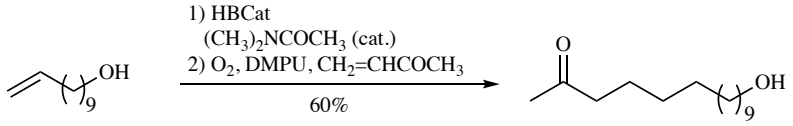
In contrast to other alkylboronic esters, *B*-alkylcatecholboranes react readily with heteroatom centered radicals such as alkoxyl radicals.[71] It was demonstrated by EPR spectroscopy that the homolytic displacement operates via the formation of a complex between *B*-methylcatecholborane and the alkoxyl radical (Scheme 20).[72]



Scheme 20. Selective generation of alkyl radicals from alkenes and catecholborane

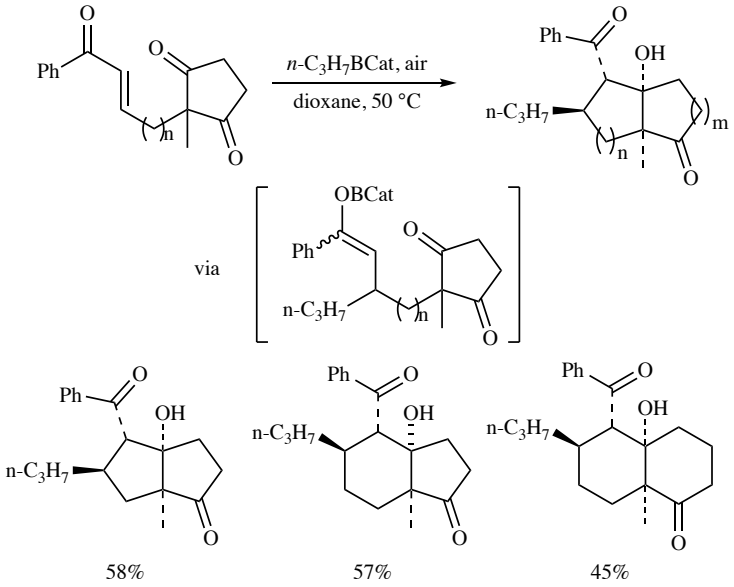
This perboryl radical adduct is stabilized by delocalization onto the aromatic ring. *B*-Alkylcatecholboranes have been introduced to improve the selectivity lacking in the cleavage of trialkylboranes. Upon reaction with an heteroatom centered radical X$^{\bullet}$, *B*-alkylcatecholboranes deliver exclusively alkyl radicals since the cleavage of B–O bonds is a reversible process, offering the possibility to generate selectively one alkyl radical from one olefin via an hydroboration process (Scheme 20).[71]

B-Alkylcatecholboranes can be used for efficient radical additions to various α,β-unsaturated aldehydes and ketones.[68,70,73] For instance, a radical-mediated reductive conjugate addition sequence was developed using enones and *B*-alkylcatecholboranes generated *in situ* by hydroboration of an alkene.[68] This procedure was employed for a 300 mmol scale synthesis of the γ-side chain of (−)-perturasinic acid (Scheme 21).[73]



Scheme 21. Reductive conjugate addition of an unprotected alkenol to methyl vinyl ketone

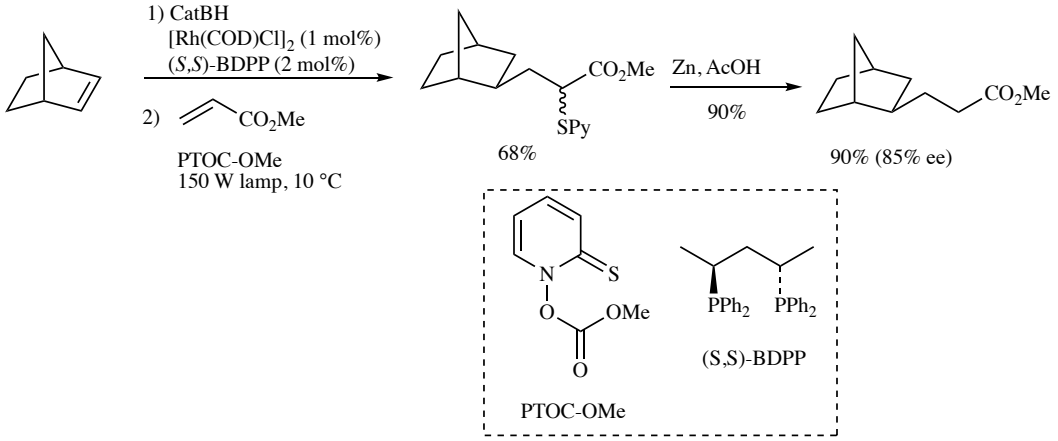
The modified Brown–Negishi reaction was investigated as well with quinone. Primary and secondary radicals gave good yields of the expected conjugate addition products, while hindered secondary and tertiary radicals favored *O*-alkylation, as it was observed with trialkylboranes.[70] *B*-Alkylcatecholboranes react efficiently with nitroxides such as TEMPO to provide the corresponding alkoxyamine.[74] Studer and coworkers applied this method to the preparation of diversely functionalized alkoxyamines derived from alkenes and polyenes.[75] A diastereoselective synthesis of monocyclic and bicyclic polysubstituted cyclohexanol involving radical conjugate addition of *B*-alkylcatecholboranes to enones was developed (Scheme 22). Mechanistic probes were investigated and support the formation of an intermediate boron enolate which would undergo an intramolecular aldol reaction.[76]



Scheme 22. Highly stereoselective conjugate addition/aldol reaction cascade

The modified Brown–Negishi and the *B*-alkylcatecholborane conjugate additions described above are limited to enone and enal traps. Other classical radical traps such as unsaturated esters, amides, and sulfones are unable to propagate a chain reaction due to the low-

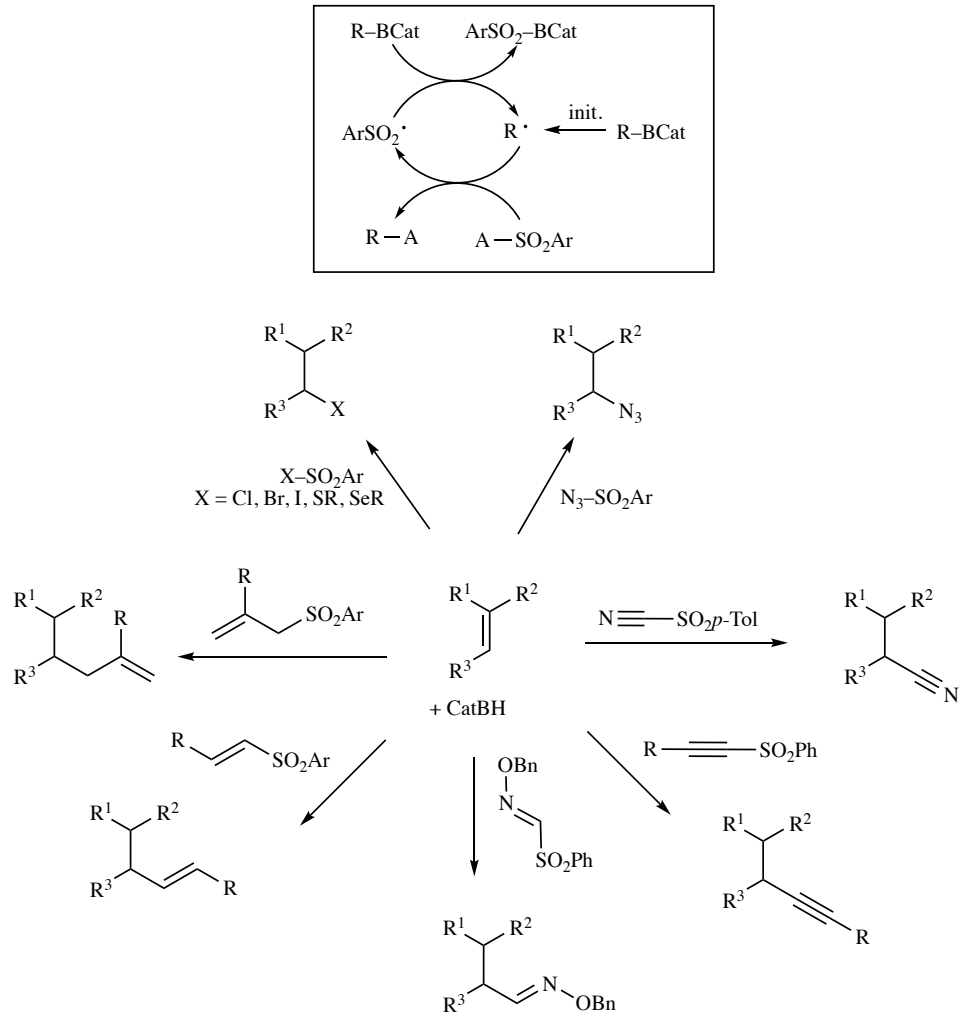
spin density at the oxygen atom of the enolyl radical intermediates. However, the use of a chain-transfer reagent such as the Barton carbonate PTOC–OMe, expands the reaction to any type of radical trap (Scheme 23).[77]



Scheme 23. Conjugate addition to methyl acrylate using a Barton carbonate chain transfer reagent

The latter proved to be a good initiator as well by irradiation with a standard 150-W tungsten lamp. Indeed, a one-pot enantioselective hydroboration-radical conjugate addition using *B*-alkylcatecholboranes as radical precursors was successfully performed.[78] For example, using norbornene and methyl methacrylate, the conjugate addition product was obtained in 68% yield and 85% ee, after desulfurization using $[Rh(COD)Cl]_2$ and the chiral diphosphine (*S,S*)-BDPP as catalyst for the hydroboration step (Scheme 23).[79] A one pot process involving chemoselective hydroboration of a diene followed by intramolecular cyclization under irradiation conditions and in the presence of the Barton carbonate PTOC–OMe was developed.[80] This approach is compatible with different functional groups such as sulfones and lactones. In contrast to the tin hydride-mediated reaction, no slow addition of the Barton carbonate carrier is needed.

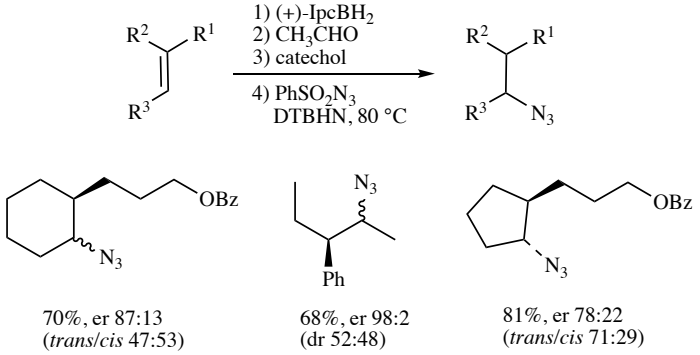
Efficient radical allylation of *B*-alkylcatecholboranes using easily available allylsulfones were developed.[79,81,82] Di-*tert*-butylhyponitrite (DTBHN) was used to initiate the radical process, and the stable phenyl sulfonyl radical generated by fragmentation was used as a chain carrier.



Scheme 24. Reaction of B-alkylcatecholboranes with sulfonyl radical traps

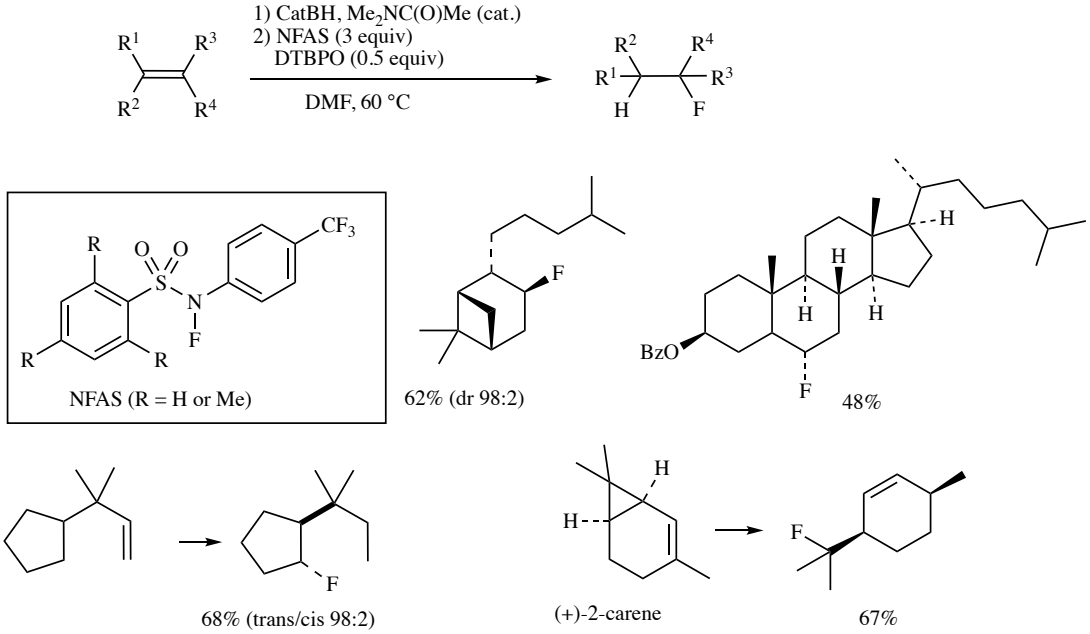
The reaction was extended to a large variety of sulfonyl radical trap and has led to efficient alkenylation,[83] alkynylation,[83] methanimination,[83] cyanation,[83] halogenation,[84] chalcogenation[84] and azidation[85] (Scheme 24).

A one-pot procedure for the enantioselective hydroazidation of non-activated trisubstituted alkenes was described (Scheme 25).[86] The control of the absolute configuration at the most substituted center of the alkene was controlled by hydroboration with monoisopinocampheylborane ($IpcBH_2$). The *in situ* generated dialkylborane was converted into *B*-alkylcatecholborane and underwent radical azidation upon treatment with benzenesulfonyl azide and DTBHN. Enantiomeric ratios up to 98:2 were obtained. The reaction was extended to the enantioselective hydroallylation, hydrohalogenation and hydrosulfurization of trisubstituted alkenes.[86]



Scheme 25. Enantioselective hydroazidation of trisubstituted alkenes

Modified *B*-alkylcatecholboranes have been reported for the generation of radicals.[87] This method involves aminocatecholborane derivatives and has been designed to facilitate purification from catechol residues. The hydrofluorination of alkenes was recently investigated using *N*-fluoro-*N*-arylsulfonamides (NFASs), a new generation of radical fluorinating agents, and good results were obtained for a wide range of substrates under mild conditions (Scheme 26).[88] The reaction proved to be efficient for secondary and tertiary *B*-alkylcatecholborane derivatives. Attempts to hydrofluorinate a terminal alkene through the formation of a primary alkyl radical afforded a secondary fluoride, which results from a 1,5-hydrogen atom transfer (HAT) process. Using (+)-2-carene, the ring-opened product was obtained in accordance with a radical mechanism.



Scheme 26. Hydrofluorination of alkenes with NFAS

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2

A General Approach to Deboronative Radical Chain Reactions with Pinacol Alkylboronic Esters

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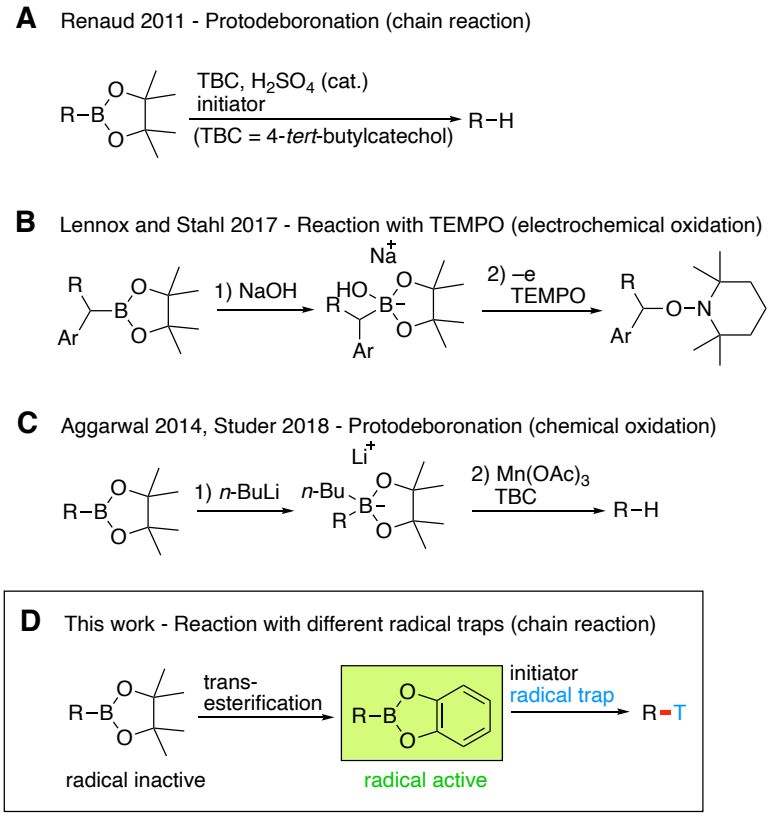
2. A general approach to deboronative radical chain reactions with pinacol alkylboronic esters

2.1 Introduction

Radical reactions are routinely applied in research laboratories involved in synthesis ranging from natural products to organic materials.[1–3] Several approaches have been developed over the years to run radical processes: non-chain reactions based on the persistent radical effect involving homolytic cleavage of a weak bond,[4] single electron transfer processes using stoichiometric or catalytic redox active agents,[5,6] photochemistry[7,8] and chain processes.[9–14] These approaches are complementary and have led to significant synthetic methods. Chain reactions are particularly attractive since, beside the reagents, they only require a substoichiometric (often tiny) amount of a radical initiator to take place. Moreover, the mildness of chain processes offers unique opportunities for applications with highly functionalized substrates. For the generation of alkyl radicals in a chain process, alkyl halides, chalcogenides, xanthates and Barton esters have been used as radical precursors. Organoboron derivatives have also been used successfully for the generation of alkyl radicals[15–18] through a nucleohomolytic substitution process.[19] For instance, trialkylboranes provide efficiently alkyl radicals but application of this type of precursor is limited to the generation of simple alkyl radicals since only one of the three alkyl groups at boron is transformed into a radical.[20] Several years ago, we demonstrated that catechol alkylboronic esters (R–Bcat) are a very efficient source of alkyl radicals.[21–23] However, more stable and easy to handle boronic acid derivatives such as pinacol alkylboronic ester (R–Bpin) are radical-inactive and therefore not suitable for the direct generation of alkyl radicals in a chain process. The generation of radicals from R–Bpin is a highly attractive process that has been tackled in the past by several groups. In an early report,[24] we have demonstrated that R–Bpin can be directly used in a radical protodeboronation processes by taking advantage of an *in situ* boron-transesterification with 4-*tert*-butylcatechol (TBC) catalyzed by sulfuric acid (Scheme 1 **A**).



Scheme 1. Strategies for the generation of alkyl radicals from stable pinacol boronic esters

In this reaction, TBC has a dual role of 1) a diol for the transesterification and, 2) a hydrogen atom source for the radical chain reaction. This approach suffers from relatively severe reaction conditions, that is, the use of 20 mol% of sulfuric acid at 80 °C, and is limited to protodeboronation. Indeed, TBC used in excess for the transesterification step outcompetes other radical traps by fast transfer of hydrogen atoms to the alkyl radicals. Non-chain approaches such as the generation of radicals through electrochemical oxidation of the ate complexes derived from R–Bpin have been described.[25,26] For instance, Lennox, Nutting and Stahl reported the generation of benzylic radicals from ArCH(R)–Bpin·NaOH complexes and were able to trap them with TEMPO (Scheme 1 **B**).[25] Similarily, Rasappan and Aggarwal and co-workers developed a radical-mediated protodeboronation reaction of R–Bpin upon treatment with phenyllithium (PhLi) to generate the corresponding ate complexes followed by an oxidative cleavage with Mn^{III} salts in the presence of TBC (Scheme 1 **C**).[27] This procedure has also been employed by Studer and co-workers,[28] who recently developed a photoredox-catalyzed protodeboronation of ate complexes derived from R–Bpin and PhLi using thiophenol as a source of hydrogen atoms.[29] Recently, Ley and co-workers described an acridinium photocatalyzed oxidative generation of alkyl radicals from R–Bpin/dimethylaminopyridine complexes using flow technology.[30] Other ate complexes such as alkyl trifluoroborates,[31–61] and

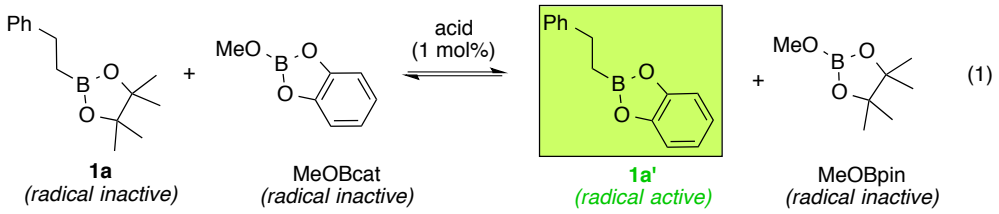
organo(triol)borates,[35,36] and boronic acids[30,57,62–65] have also been successfully oxidized to deliver the corresponding alkyl radicals using either electrochemical, chemical, or photoredox-catalyzed oxidation.[66] Based on the preliminary results described in Scheme 1 **A**, we report here particularly simple conditions to furnish radicals from a variety of different pinacol alkylboronic esters made possible by an *in situ* transesterification. This approach is not limited to protodeboronation; a broad range of C–X and C–C bond forming reactions using a variety of radical traps are possible (Scheme 1 **D**).

2.2 Results and discussion

2.2.1 Transesterification

Finding a suitable transesterification method was the key element of our strategy. The most obvious method, that is, the transesterification with catechol has already been reported by us[24] but was rapidly abandoned since residual catechol acts as an excellent source of hydrogen atoms in a competitive radical protodeboronation reaction.[67,68] To circumvent the undesired protodeboronation, alternative procedures for the transesterifications that do not involve free catechol were examined. Transesterification of pinacol alkylboronate R–Bpin with catechol boronic or boric esters was a promising alternative since no free catechol will be present in solution. To avoid the presence of two different radical precursors in the reaction medium, it is important to use radical-inactive catechol boronic or boric esters. The boronic esters catechol methylboronic ester (Me–Bcat) and catechol phenylboronic ester (Ph–Bcat) were tested first, both of them are radical-inactive, that is, unable to generate the corresponding highly reactive methyl and phenyl radicals. Under acid catalysis (4 mol% CF_3SO_3H), transesterification took place with both boronic esters. However, better results in term of catalyst loading and efficacy were obtained with catechol methyl borate (MeO–Bcat). The transesterification between pinacol 2-phenylethylboronic ester **1a** and MeO–Bcat was investigated in a more systematic way [Eq. (1)]. The reaction was followed by ^{1}H NMR and the results are summarized in Table 1 (see the Supporting Information for NMR spectra).

*Table 1. Transesterification of **1a** with MeO–Bcat (1 equivalent)*



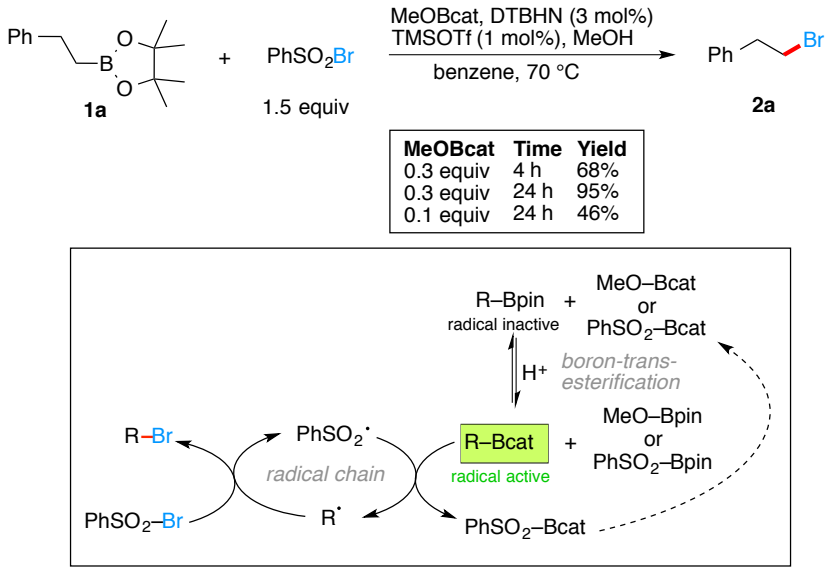
Entry	Acid[a]	Time	**1a**/**1a'**
1	–	4 h	100:0
2	CF_3CO_2H	2 h	88:12
3	CF_3CO_2H	4 h	79:21
4	CH_3SO_3H	2 h	85:15
5	CH_3SO_3H	4 h	68:32
6	CF_3SO_3H	2 h	46:54
7	CF_3SO_3H	4 h	45:55
8	CF_3SO_3H	45 min	46:54
9	CF_3SO_3H	30 min	49:51
10	CF_3SO_3H	15 min	63:37

[a] Using 1 mol% of the acid at 80 °C in [D_6]benzene. The ratio of **1a**/**1a'** was determined by integrations of the diagnostic α-boryl peaks in ^{1}H NMR (**1a**: 1.26 ppm (t, J = 8.0 Hz, 2H); **1a'**: 1.41 ppm (t, J = 8.2 Hz, 2H)).

In the absence of acid, no reaction took place (entry 1). Trifluoroacetic acid and methanesulfonic acid (1 mol%) were both able to catalyze the transesterification. However, after 4 h, the equilibrium was not reached (Table 1, entries 2–5). Interestingly, trifluoromethanesulfonic acid generated *in situ* from TMS triflate and methanol provided a 46:54 mixture of **1a**/**1a'** after 2 h (Table 1, entry 6). Longer reaction times did not alter the ratio, thus demonstrating that the thermodynamic equilibrium was reached (Table 1, entry 7). Decreasing the reaction times showed that the equilibrium was reached by 45 minutes (Table 1, entries 8–10). Based on these results, transesterification with MeO–Bcat catalyzed by *in situ* generated triflic acid was adopted for the development of the one-pot transesterification/radical process.

2.2.2 Deboronative halogenation and chalcogenation

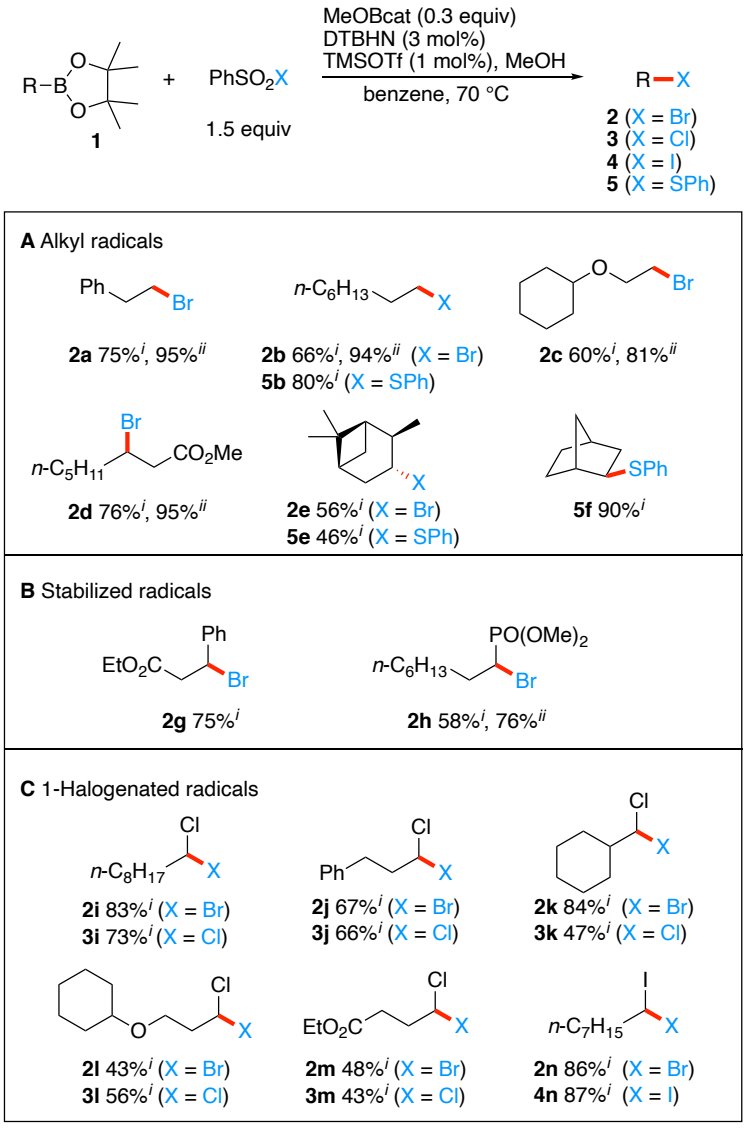
According to previous results obtained with a pure R–Bcat derivative,[69] the radical bromination of **1a** with benzenesulfonyl bromide initiated by di-*tert*-butylhyponitrite (DTBHN)[70] was examined first. Gratifyingly, it was immediately observed that only a substoichiometric amount of MeO–Bcat was necessary to run the reaction to completion (Scheme 2). Using 1 mol% of TMSOTf and MeOH and 0.3 equivalent of MeO–Bcat afforded the desired bromide **2a** in 68% yield after 4 h. The yield increased to 95% after 24 h. Using a smaller amount of MeO–Bcat (0.1 equiv) was detrimental to the yield. A potential reaction mechanism is provided in Scheme 2 (frame). The radical chain process is coupled with a boron-transesterification reaction. The fact that only a substoichiometric of the radically inactive MeO–Bcat is necessary to reach high conversion and yields suggests that the $PhSO_2$–Bcat generated in the radical chain reaction also acts as a transesterification reagent.[71]



*Scheme 2. Optimization of the radical deboronative bromination of **1a***

The optimized reaction conditions were then tested with a variety of substrates and with different halogenating and chalcogenating radical traps such as benzenesulfonyl halides and *S*-phenyl benzenethiosulfonate.[69] The results are summarized in Scheme 3. The reaction worked for a broad range of substrates such as primary (**1a**–**1c**) and secondary (**1d**–**1f**) alkylboronic esters (Scheme 3 **A**). Boronic esters delivering stabilized benzylic (**1g**) and α-phosphonyl (**1h**) radicals provided the expected bromides **2g** and **2h** (Scheme 3 **B**). The halogenation of radicals derived from α-chlorinated pinacol boronic esters **1i**–**1m**, which are easily prepared through Matteson homologation of pinacol alkylboronic ester using lithiated dichloromethane,

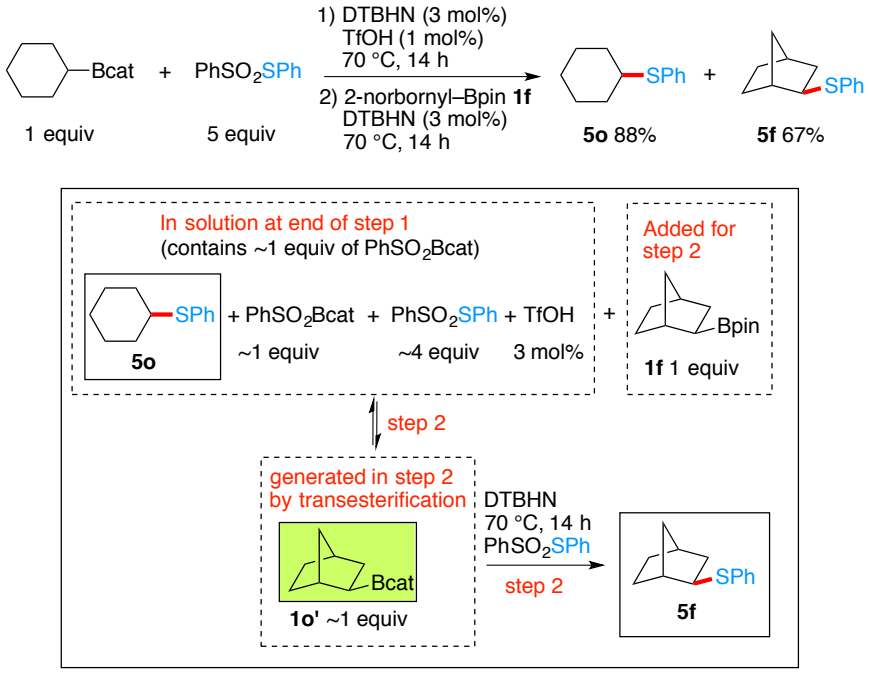
proceeded efficiently (Scheme 3 **C**). Overall, this reaction sequence can convert a boryl group into either a dichloromethyl, a bromochloromethyl, or an iodochloromethyl group – three transformations that cannot be achieved easily using known chemistry. The α-iodinated boronic ester **1n** was brominated to *gem*-bromoiodo compound **2n** in 86% yield. This example demonstrates further that this method is very valuable and general for the preparation of unsymmetrical *gem*-dihalides (see formation of compounds **2i**–**n**). Finally, the iodination of **1n** provided the symmetrical *gem*-diiodo derivative **4n** in excellent yield.



Scheme 3. Deboronative halogenation and chalcogenation of pinacol boronic esters. [i] Yield of isolated product. [ii] Yield determined by quantitative GC analysis

As mentioned earlier (Scheme 2), all these reactions require only a substoichiometric amount (0.3 equivalent) of the radical inactive transesterification reagent MeO–Bcat. This

suggest that $PhSO_2$–Bcat resulting from the reaction of the benzenesulfonyl radical with in situ formed R–Bcat also acts as a transesterification reagent (see mechanism depicted in Scheme 2). This point was demonstrated by running a control experiment where the only source of catechol is $PhSO_2$–Bcat, which was generated by reacting Cy–Bcat (**1o'**) with $PhSO_2SPh$ (Scheme 4).[72] In a first phase, pure **1o'** was reacted for 14 h with a five-fold excess of $PhSO_2SPh$ to afford Cy–SPh (**5o**) and $PhSO_2$–Bcat as well as unreacted $PhSO_2SPh$. At this point, the radical-inactive 2-norbornyl–Bpin (**1f**) was added to the reaction mixture and the reaction was heated in the presence of DTBHN for another 14 h before product isolation. Beside Cy–SPh (**5o**, 88%) formed during the first phase of the reaction, 2-nornornyl–SPh (**5f**) was isolated in 67% yield, thus demonstrating that $PhSO_2$–Bcat is involved in the transesterification process.

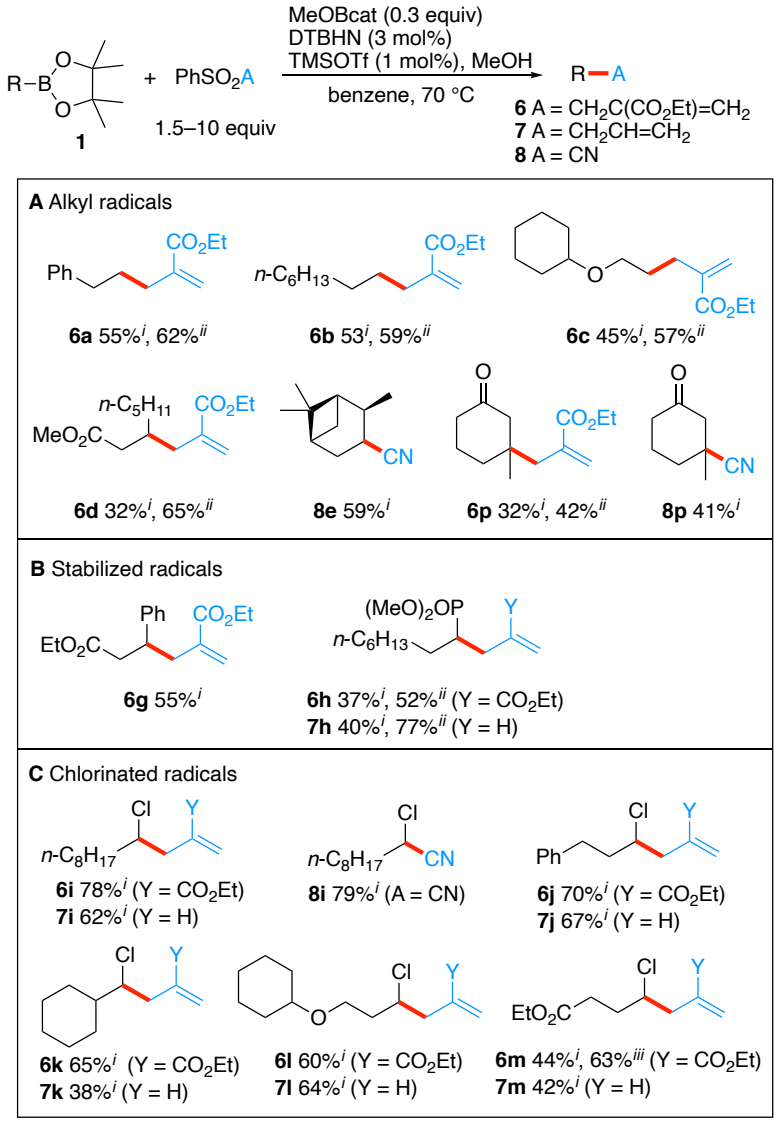


*Scheme 4. Mechanistic study of the sulfurization of 2-norbornyl–Bpin **1f** using in situ generated $PhSO_2$–Bcat as a transesterification reagent*

2.2.3 Deboronative alkylation

Formation of C–C bonds using different sulfonyl radical traps was investigated next. Simples alkyl radicals derived from **1a–d** provided the desired allylated products **6a–d** in moderate to good yields using 1.5 equivalents of the trap (Scheme 5 **A**). The tertiary β-keto radical derived from **1o** gave **6p** in modest yield. The cyanation of **1e** and **1o** proceeded well to give **8e** and **8p**, respectively. Stabilized radicals derived from **1g** and **1h** gave the expected

allylated products **6–h,** and **7h** in satisfactory yields (Scheme 5 **B**). Finally, the α-chlorinated radicals derived from **1i–1l** reacted well with electron deficient and electron rich allylsulfones leading to **6i–6m** and **7j–m**, respectively (Scheme 5 **C**). The deboronative cyanation of **1i** afforded the α-chloronitrile **8i** in 79% yield. Interestingly, most of these reactions have been performed using a small excess of the radical trap (1.5 equivalents), leaving room for optimization when structurally more complex organoboranes are used.

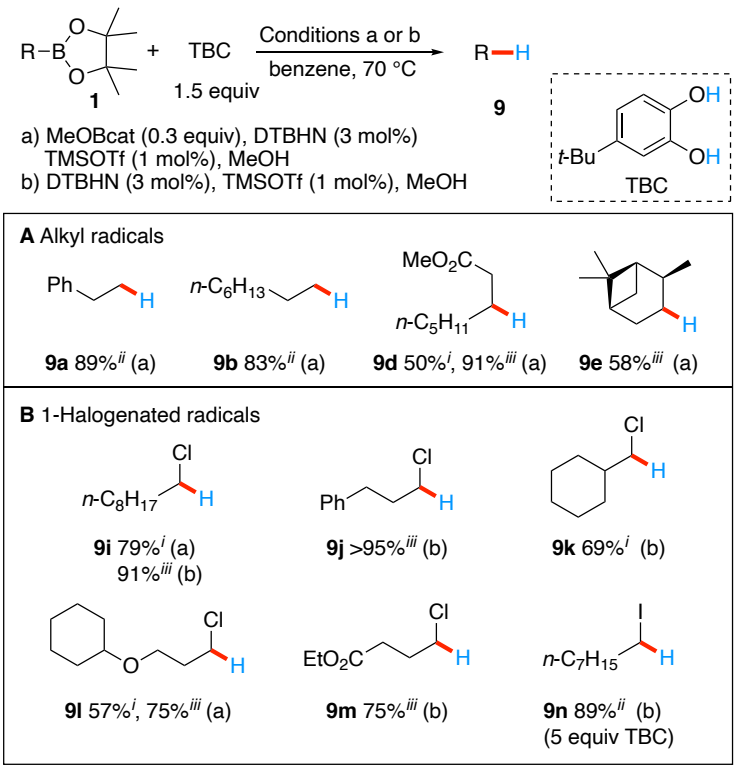


Scheme 5. Deboronative alkylation of pinacol boronic esters using sulfone radical traps. [i] Yield of isolated product. [ii] Yield determined by quantitative GC analysis. [iii] Using 10 equivalents of the trap. [iv] Yield corrected by ^{1}H NMR to account for inseparable residual radical trap

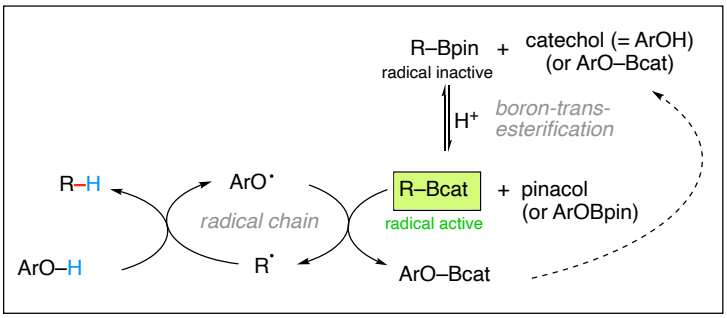
2.2.4 Protodeboronation

Finally, the protodeboronation of pinacol alkylboronic esters was investigated under our mild radical chain reaction conditions using TBC as a source of hydrogen atoms (Scheme 6, conditions a).[73] Under these conditions, primary and secondary alkyl boronates are efficiently converted to the protodeboronated products **9**–**b** and **9d**–**e** (Scheme 6 A). The α-chlorinated boronates **1i**–**1m** provided the protodeboronated products **9i**–**9m** in high yields. Remarkably, the α-iodoboronate **1n** gave **9n** in 89% yield, further demonstrating the very high level of chemoselectivity of this radical protodeboronation process. The protodeboronation with TBC on α-halogenated boronates **1i**–**1n** were run without MeO–Bcat (Scheme 6, conditions b). These substrates were protodeboronated without triflic acid catalysis with only slight reductions in yield. The higher reactivity of the α-haloalkylboronic esters relative to non-halogenated alkylboronic esters is attributed to the higher acidity of the boron atom that facilitates the transesterification.[74]

A simplified mechanism for the radical protodeborylation process (Scheme 6, conditions b) is described in Scheme 7. For clarity, the mechanism is depicted with catechol instead of TBC (the 4-*tert*-butyl substituent being a spectator substituent). The boron-transesterification process directly involves catechol (at least at the beginning of the reaction) and the *in situ* generated ArO–Bcat. The mechanism of the radical-chain protodeboronation has been previously discussed more exhaustively.[24,75]



Scheme 6. Protodeboronation of pinacol boronic esters. [i] Yield of isolated product. [ii] Yield determined by quantitative GC analysis. [iii] ^{1}H NMR yield

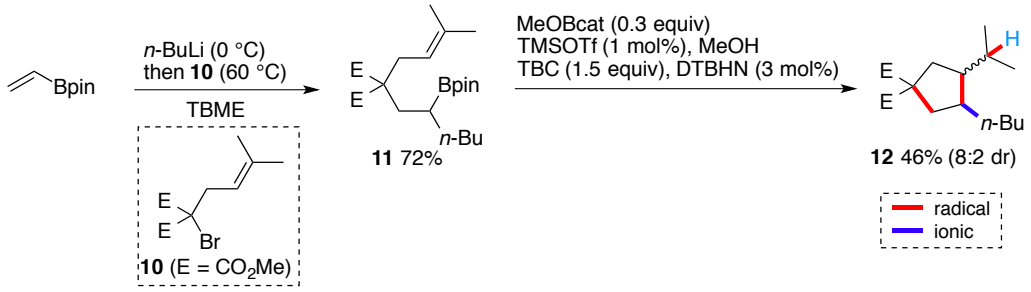


Scheme 7. Simplified mechanism for the protodeboronation reaction. For clarity, catechol and TBC are not differentiated; ArOH can be either catechol

2.2.5 Merging radical and non-radical boron chemistry

Finally, to demonstrate the potential of merging the rich chemistry of boronic ester with radical chemistry, we prepared the 5-membered-ring **12** through a two-step procedure involving a three-component coupling reaction[76] between dimethyl (3,3-dimethylallyl)malonic acid, pinacol vinylboronic ester, and *n*-butyllithium followed by deboronative radical cyclization (Scheme 8). The reported procedure for the three-component coupling process[77] was

significantly improved by avoiding the use of any radical initiator. The chain reaction is presumably initiated by means of electron transfer from the ate complex to the α-bromomalonate. Overall, three new C—C bonds and one C—H bond are formed. The bonds highlighted in red are formed by radical processes and those in blue by an ionic 1,2-metallate (or anionotropic) rearrangement.



Scheme 8. 5-Membered ring synthesis by combining radical and ionic chemistry of pinacol boronic esters

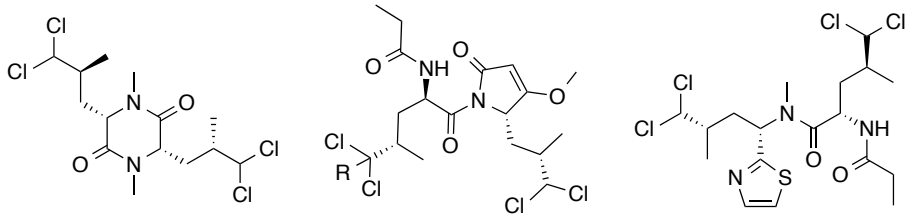
2.3 Conclusion

We have developed a simple and efficient set of radical chain reactions starting from air stable pinacol alkylboronic esters. Activation of the radical inactive R–Bpin through transesterification with the boric ester MeO–Bcat under acid catalysis provides access to a broad range of radical precursors. Merging the rich chemistry of boronic esters with radical reactions is expected to open a tremendous number of applications for the synthesis and derivatization of complex target molecules such as natural products and other pharmacologically relevant compounds.

2.4 Generation of dichloromethyl radicals (unpublished)

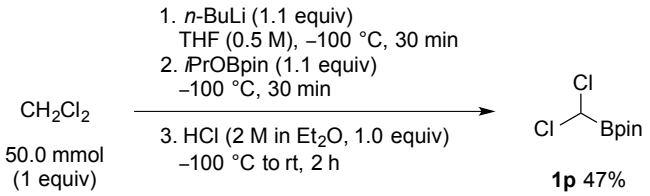
Eventually, the potential of using α-chlorinated R–Bpin as radical precursors was further investigated with the generation of *gem*-dichloromethyl radicals. Besides its ubiquity and peculiar role in many bioactive natural compounds (Scheme 9),[78,79,80,81,82,83,84] dichloromethyl units are of great interest for further functionalization of its electrophilic carbon. Furthermore,

the addition of a dichloromethyl radical unit allows the introduction of a C1-synthon while simultaneously adding chemical value to the backbone for further functionalization.

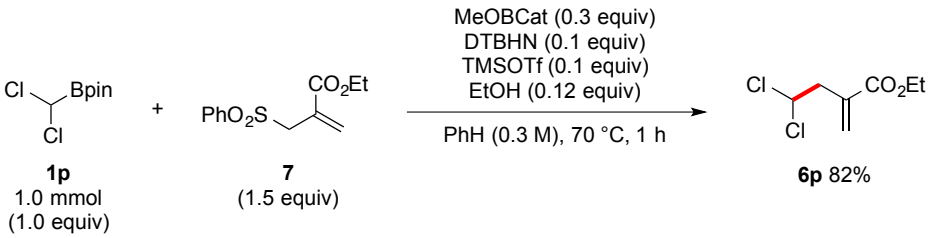


Scheme 9. Exemples of gem-dichlorinated natural products

Considering the synthetic utility of the dichloromethyl radical, there is little precedent reported for its synthesis with obvious restrictions in terms of synthetic transformations.[85,86,87,88,89,90] Therefore, we hypothesized that by using our radical deboronative approach starting from a (dichloromethyl)pinacol boronic ester derivative, one could generate the corresponding dichloromethyl radical. In this regard, the radical precursor **1p** was prepared by hydrolysis of a boron ate-complex formed from the reaction of iPrO–Bpin with an *in situ* generated (dichloromethyl)lithium carbenoid (Scheme 10). Next, the resulting (dichloromethyl)pinacol boronic ester was engaged in the radical deboronative allylation chain process and furnished **6p** in excellent yield (Scheme 11). This successful result opens the door to the development of new deboronative radical chain processes to access invaluable dichloromethyl containing compounds.



*Scheme 10. Synthesis of the (dichloromethyl)pinacol boronic ester **1p** (yield of isolated product)*



*Scheme 11. Radical deboronative allylation of **1p** to furnish **6p** (yield of isolated product)*

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Experimental Part

Contents

1 General and Instrumentation

Glassware and reaction techniques: Unless otherwise stated, all glassware was flame-dried or oven-dried, cooled under vacuum, and back-filled with nitrogen or argon; then the reactions were run under that inert atmosphere and additions of solids were performed under a positive pressure of that inert atmosphere. Unless otherwise stated, all yields are isolated yields. Room temperatures (rt) were generally in the range 21–25 °C.

Solvents: Dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene for reactions were filtered over a column of dried alumina under a positive pressure of argon. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. All water used for solutions and work-ups was deionized water.

Reagents and chemicals: All reagents and chemicals used were commercial and used without further purification unless specified below. The compounds **9a** (CAS number: 100-41-4), **9b** (CAS number: 111-65-9), **9e** (CAS number: 473-55-2), and **9n** (CAS number: 629-27-6), were commercially available and purchased from Aldrich in order to perform GC or NMR yields.

Column chromatography: All chromatographic purifications were flash (ca. 2-3 atm. of pressurized air) column chromatography (FCC) on silica gel (Macherey-Nagel Silica 60, 0.04 – 0.063 mm) or neutral aluminium oxide (CAMAG 507 – C – I neutral).

Thin layer chromatography (TLC): Silicycle glass backed TLC extra hard layer, 259 µm, 60 Å, F-254 Silica gel 60 Å (F-254) and *Macherey-Nagel* SIL G/UV254, 0.25 mm analytical plates were used for TLC. Revelation was done firstly by non-destructive visualization under a UV lamp (254 nm) and iodine suspended in silica gel; destructive revelation was performed with staining-solutions of either potassium permanganate ($KMnO_4$), cerium molybdate (CAM), *p*-anisaldehyde, phosphomolybdic acid ($H_3PMo_{12}O_{40}$), or cerium sulfate ($Ce(SO_4)_2$), followed by heating.

NMR: The NMR experiments were performed on a Bruker Avance-300 spectrometer operating at a resonance frequency of 300.18 MHz for ^{1}H nuclei, 75.48 MHz for ^{13}C and 96 MHz for ^{11}B nuclei. ^{11}B NMR spectra were calibrated using $Et_2O.BF_3$ (0.0 ppm) as an external reference. Chemical shifts are reported in units of δ (ppm) using the internal standard residual $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR spectra and δ = 77.16 ppm for ^{13}C NMR spectra), or TMS (δ = 0.00 ppm for ^{1}H NMR spectra and δ = 0.00 ppm for ^{13}C NMR spectra). Due to coupling to the quadrupolar ^{11}B and ^{10}B nuclei, the carbons linked to boron atoms generally give a broad signal in ^{13}C NMR, sometimes not detected. The following abbreviations were used to explain the multiplicities: s

= singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. Referencing and common impurities were assigned by common standards.[1,2]

NMR yields were determined using 1,4-dimethoxybenzene (s, 6.74 ppm, 4H; s, 3.67 ppm, 6H) as an internal standard. The standard was added to the crude residue after work-up, dissolved in $CDCl_3$ by swirling and sonication for 5 mins in order to have a homogenous mixture, and an aliquot was taken to be analyzed by ^1H NMR.

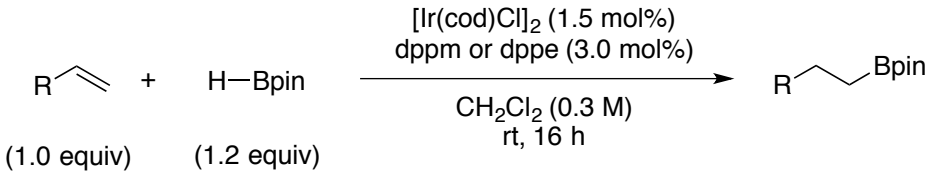
GC: GC analyses were carried out on a Thermo Electron Trace GC ULTRA instrument fitted with a Macherey-Nagel Optima delta-3-0.25 µm capillary column (20 m, 0.25 mm). Gas carrier: He 1.4 mL/min; injector: 220 °C split mode; detector: FID 280 °C, H2 35 mL/min, air 350 mL/min. Infrared spectra were recorded on a Jasco FT/IR-4700 Spectrometer and are reported in wave numbers (cm^{-1}).

MS: HRMS analyses and elemental composition determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using ESI and NSI mode at the University of Bern. When ESI and NSI didn't provide the successful ionization, HRMS was performed at the University of Zürich with a Bruker maXis QTof high resolution mass spectrometer (APCI mode) and Thermo DFS (ThermoFisher Scientific) double-focusing magnetic sector mass spectrometer (EI and CI modes).

IR: Infrared spectra were recorded neat equipped with a diamond ATR System and are reported in wave numbers (cm^{-1}). Reported are the characteristic signals only (with decreasing wave number).

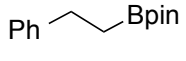
2 Experimental Procedures and Characterizations for the Synthesis of Reagents and Substrates

2.1 General Procedure 1 (GP1): Iridium catalyzed hydroboration of terminal alkenes to furnish 1a–c, SI-1, and 1f[3]



A one-neck, round-bottom flask was charged with $[Ir(cod)Cl]_2$ (1.5 mol%) and ethylenebis(diphenylphosphine) (dppe) or methylenebis(diphenylphosphine) (dppm) (3.0 mol%) in a glove-box. DCM (3.0 mL/mmol), pinacolborane (1.2 equiv), and the alkene (1.0 equiv) were added successively to the flask at 0 °C, and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched with MeOH (1.0 mL/mmol) and H_2O (3.0 mL/mmol), and the product was extracted twice with Et_2O (4.0 mL/mmol). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude residue.

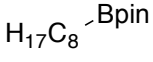
4,4,5,5-Tetramethyl-2-(2-phenylethyl)-1,3,2-dioxaborolane (1a)



$C_{14}H_{21}BO_2$
MW: 232.16

From styrene (5.21 g, 50.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **1a** as a colorless liquid (10.94 g, 47.1 mmol, 84%). Spectral and physical data were in accordance with the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.11 (m, 5H), 2.74 (dd, $J_A = J_B$ = 8.2 Hz, 2H), 1.20 (s, 12H), 1.14 (dd, $J_A = J_B$ = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 128.2, 128.0, 125.5, 83.0, 29.9, 24.8. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9.

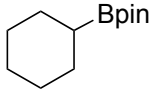
4,4,5,5-Tetramethyl-2-octyl-1,3,2-dioxaborolane (1b)



$C_{14}H_{29}BO_2$
MW: 240.23

From 1-octene (4.50 g, 40.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **1b** as a colorless oil (8.94 g, 37.2 mmol, 93%). Spectral and physical data were in accordance with the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 – 1.38 (m, 2H), 1.32 – 1.24 (m, 22H), 0.89 – 0.85 (m, 3H), 0.77 (app t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.8, 32.5, 31.9, 29.4, 29.3, 24.8, 24.0, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.1.

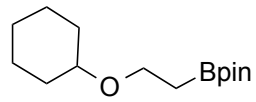
2-Cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-1)



$C_{12}H_{23}BO_2$
MW: 210.18

From cyclohexene (821 mg, 10.0 mmol) following **GP1**. The residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **SI-1** as a colorless liquid (1.97 g, 9.4 mmol, 94%). Spectral and physical data were in accordance with the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 – 1.58 (m, 5H), 1.36 – 1.29 (m, 5H), 1.23 (s, 12H), 1.03 – 0.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.7, 28.0, 27.2, 26.8, 24.8. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.0.

2-[2-(Cyclohexoxy)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1c)



$C_{14}H_{27}BO_3$
MW: 254.21

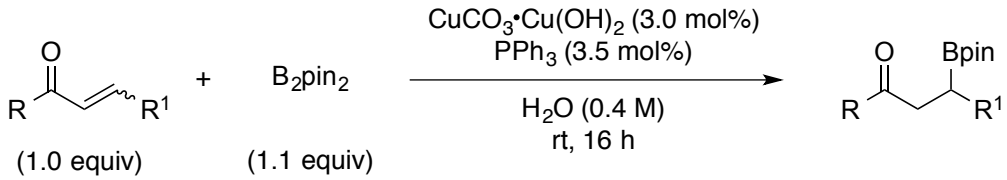
From vinyloxycyclohexane (2.52 g, 20.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **1c** as a colorless liquid (3.44 g, 13.5 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (t, J = 7.9 Hz, 2H), 3.22 (hept, J = 3.9 Hz, 1H), 1.93 – 1.89 (m, 2H), 1.73 – 1.71 (m, 2H), 1.53 – 1.51 (m, 1H), 1.27 – 1.21 (m, 17H), 1.14 (t, J = 7.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.0, 77.2, 64.3, 32.4, 25.9, 24.8, 24.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.4. IR (neat): 2978, 2930, 2856, 1367, 1353, 1318, 1145, 1090, 967, 848 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{28}O_3B$ $[M+H]^+$: 255.2124; found: 255.2126.

2-((1R,2R,4R)-Bicyclo[2.2.1]heptan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1f)

$C_{13}H_{23}BO_2$
MW: 222.14

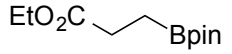
From norbornene (942 mg, 10.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **1f** as a colorless oil (1.58 g, 7.1 mmol, 71%). Spectral and physical data were in accordance with the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 – 2.18 (m, 2H), 1.58 – 1.44 (m, 3H), 1.34 (ddd, J = 11.7, 10.0, 1.9 Hz, 1H), 1.28 – 1.14 (m, 16H), 0.91 – 0.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.9, 38.9, 38.3, 36.8, 32.4, 32.3, 29.4, 24.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.0.

2.2 General Procedure 2 (GP2): Borylation of Michael acceptors to furnish SI-2, 1d, 1g, and 1o[4]



A two-necks, round-bottom flask was charged with basic $CuCO_3$ catalyst (3.0 mol%) and triphenylphosphine (3.5 mol%) under inert atmosphere. Deionized water (0.4 M) was added and the reaction mixture was stirred at rt for 15 min. Bis(pinacolato)diboron (1.1 equiv) was then added in one portion at rt, and stirring was continued for 30 min. The corresponding Michael acceptor (1.0 equiv) was added to the reaction mixture and stirring was continued at rt for further 16 h. The reaction mixture was diluted with brine and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduce pressure.

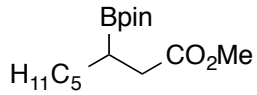
Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (SI-2)



$C_{11}H_{21}BO_4$
MW: 228.15

From ethyl acrylate (1.10 g, 11.0 mmol) following **GP2**. The residue was purified by FCC on silica gel (heptanes/EtOAc 95:5 to 9:1) to afford **SI-2** as a colorless oil (2.36 g, 10.4 mmol, 94%). Spectral and physical data were in accordance with the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.27 – 1.22 (m, 15H), 1.02 (app t, *J* = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 83.2, 60.2, 28.8, 24.8, 14.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.7.

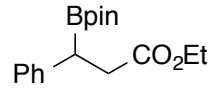
Methyl 3-(*B*-pinacolboryl)octanoate (1d)



$C_{15}H_{29}BO_4$
MW: 284.20

From methyl 2-octenoate (1.73 mL, 10.0 mmol) following **GP2**. The residue was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **1d** as a colorless oil (2.01 g, 7.1 mmol, 71%). Spectral and physical data were in accordance with the literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.49 – 2.30 (m, 2H), 1.44 – 1.42 (m, 1H), 1.23 – 1.22 (m, 20H), 0.85 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 83.2, 51.4, 35.7, 32.0, 30.6, 28.5, 24.9, 24.8, 22.6, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.7.

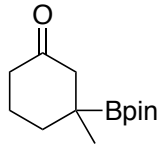
Ethyl 3-phenyl-3-(*B*-pinacolboryl)propanoate (1g)



$C_{17}H_{25}BO_4$
MW: 304.19

From ethyl cinnamate (1.68 mL, 10.0 mmol) following **GP2**. The residue was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **1g** as colorless crystals (3.04 g, 10.0 mmol, 76%). Spectral and physical data were in accordance with the literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 6.97 (m, 5H), 4.14 – 3.95 (m, 2H), 2.87 – 2.50 (m, 3H), 1.21 – 1.04 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 141.5, 128.6, 128.3, 125.8, 83.6, 60.5, 37.5, 24.7, 24.6, 14.4. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.0.

3-Methyl-3-(*B*-pinacolboryl)cyclohexan-1-one (1o)



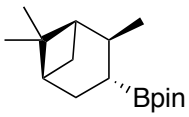
$C_{13}H_{23}BO_3$
MW: 238.13

From 3-methylcyclohex-2-en-1-one (1.13 mL, 10.0 mmol) following **GP2**. The residue was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **1o** as a beige crystalline solid (1.65 g, 6.9 mmol, 69%). Spectral and physical data were in accordance with the literature.[4] A sample was crystallized from heptanes to give white-translucent crystals, m.p. = 68.8 – 70.3 °C (heptanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (dt, J = 13.8, 1.4 Hz, 1H), 2.38 – 2.12 (m, 2H), 2.06 – 1.88 (m, 3H), 1.87 – 1.69 (m, 1H), 1.48 – 1.33 (m, 1H), 1.20 (s, 12H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 83.6, 50.8, 41.3, 34.3, 24.74, 24.67, 24.3, 23.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.0.

2.3 Other Methods: Hydroborations to furnish 1e and SI-3

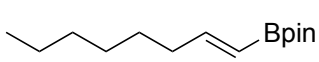
4,4,5,5-Tetramethyl-2-((1*R*,2*S*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1,3,2-dioxaborolane (1e)[6]



$C_{16}H_{29}BO_2$
MW: 264.23

To a two-neck, round-bottom flask was loaded boron trichloride (22 mL, 22.0 mmol, 1.0 M in CH_2Cl_2, 1.1 equiv) under inert atmosphere. A mixture of (+)-α-pinene (3.18 mL, 20.0 mmol, 1.0 equiv) and triethylsilane (3.17 mL, 20.0 mmol, 1.0 equiv) dissolved in CH_2Cl_2 (50 mL, 0.4 M) was added dropwise to the boron trichloride at rt. After 1 h, pinacol (4.3 g, 40.0 mmol, 2.0 equiv) was added portionwise at rt and the contents were stirred for another 12 h. The volatiles were removed *in vacuo* and the residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **1e** as a colorless liquid (4.7 g, 17.7 mmol, 88%). Spectral and physical data were in accordance with the literature.[7] $[\alpha]_D^{20}$ – 11.7° (*c* 1.00, $CHCl_3$ (HPLC grade, stabilized on EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 – 2.23 (m, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 1.95 (m, 1H), 1.93 – 1.79 (m, 2H), 1.78 – 1.71 (m, 1H), 1.23 (s, 12H), 1.23 – 1.20 (m, 1H), 1.16 (s, 2H), 1.03 (s, 3H), 1.02 (d, J = 6.1 Hz, 3H), 0.81 (d, J = 9.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.9, 48.1, 41.4, 38.7, 38.3, 34.2, 28.8, 28.6, 24.84, 24.79, 23.3, 22.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.7.

4,4,5,5-Tetramethyl-2-[(*E*)-oct-1-enyl]-1,3,2-dioxaborolane (SI-3)[8]

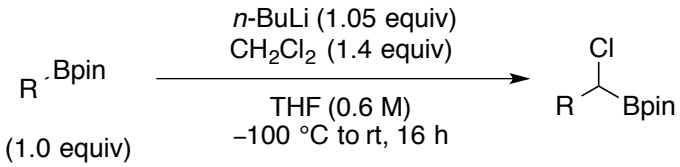


$C_{14}H_{27}BO_2$
MW: 238.21

Pinacolborane (2.27 ml, 15.8 mmol, 1.05 equiv) was added at 0°C to neat mixture of Schwartz' reagent (387 mg, 1.5 mmol, 10 mol%) and 1-octyne (2.21 mL, 15.0 mmol, 1.0 equiv). Then triethylamine (210 µL, 1.5 mmol, 10 mol%) was added and the mixture was heated at 40 °C for 17 h and cooled to rt. The reaction mixture was poured in H_2O (20 ml) and extracted with Et_2O (3x20 ml). The combined organic layers were washed with brine (30 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by FCC on silica gel (*n*-pentane/EtOAc 98:2) to afford **SI-3** as a colorless liquid (2.93 g, 12.3 mmol, 82%). Spectral and physical data were in accordance with the literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (dt, J = 17.9, 6.4

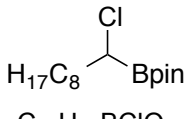
Hz, 1H), 5.41 (dt, J = 17.9, 1.5 Hz, 1H), 2.18 – 2.10 (m, 2H), 1.43 – 1.24 (m, 20H), 0.87 (app t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 83.1, 36.0, 31.9, 29.1, 28.3, 24.9, 22.7, 14.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.9.

2.4 General Procedure 3 (GP3): Matteson homologation to furnish 1i–m[9]



A one-neck, round-bottom flask was charged with CH_2Cl_2 (1.4 equiv) and THF (0.6 M) and cooled to –100 °C in a 95% ethanol/liquid nitrogen slush bath. The solution was stirred and *n*-butyllithium (1.05 equiv) was added dropwise by bringing the tip of the syringe needle to within about 5 mm of the surface of the cold solution. After 30 min, a solution of alkyl pinacolboronic ester (1.0 equiv) in Et_2O (2 mL) was added in one portion to the mixture and the contents were allowed to warm up to rt and stirring was continued overnight. CH_2Cl_2 was added to precipitate the lithium chloride. The solution was filtered over cotton, and the volatiles were removed *in vacuo*.

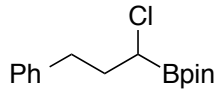
2-(1-Chlorononyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1i)



$C_{15}H_{30}BClO_2$
MW: 288.20

From **1b** (5.76 g, 24.0 mmol) following **GP3**. The product was purified by vacuum distillation (85 °C head, 1×10^{-2} mbar) to afford **1i** as a colorless oil (5.24 g, 18.2 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (dd, J = 7.9, 6.9 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.50 – 1.24 (m, 24H), 0.88 (app t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.3 (2C), 34.1, 31.9, 29.4, 29.2, 29.1, 27.3, 24.61, 24.58, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.4. IR (neat): 2978, 2924, 2854, 1380, 1372, 1340, 1140, 967, 847, 673 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{30}O_2BClNa$ [M+Na]+: 311.1919; found: 311.1920.

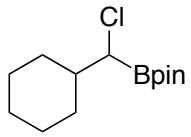
2-(1-Chloro-3-phenyl-propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane (1j)



$C_{15}H_{22}BClO_2$
MW: 280.14

From **1a** (5.80 g, 25.0 mmol) following **GP3**. The product was purified by vacuum distillation (110 °C, 2.0×10^{-3} mbar) to afford **1j** as a colorless oil (3.56 g, 12.7 mmol, 51%). Spectral and physical data were in accordance with the literature.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 3.41 (app t, *J* = 7.4 Hz, 1H), 2.87 – 2.70 (m, 2H), 2.12 (app q, *J* = 7.7 Hz, 2H), 1.28 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 128.6, 128.4, 126.0, 84.5, 35.7, 33.3, 24.62, 24.61. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.4.

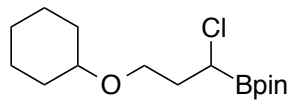
2-[Chloro(cyclohexyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1k)



$C_{13}H_{24}BClO_2$
MW: 258.16

From **SI-1** (1.94 g, 9.2 mmol) following **GP3**. The product was purified by vacuum distillation (75 °C, 8.0×10^{-3} mbar) to afford **1k** as a colorless oil (1.35 g, 5.2 mmol, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (d, *J* = 7.4 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.82 – 1.60 (m, 5H), 1.35 – 0.98 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.4, 41.4, 31.0, 30.7, 26.4, 26.3, 26.1, 24.8, 24.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) calcd. for $C_{13}H_{24}O_2BClNa$ [M+Na]+: 281.1440; found: 281.1450.

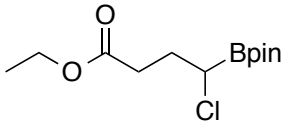
2-[1-Chloro-3-(cyclohexoxy)propyl]-4,4,5,5-tetramethyl-1,3,2-di-Oxaborolane (1l)



$C_{15}H_{28}BClO_3$
MW: 302.18

From **1c** (2.54 g, 10.0 mmol) following **GP3**. The product was purified by vacuum distillation (95 °C, 1.2×10^{-3} mbar) to afford **1l** as a colorless oil (1.52 g, 5.0 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 – 3.55 (m, 3H), 3.26 – 3.18 (m, 1H), 2.09 – 1.88 (m, 4H), 1.77 – 1.65 (m, 2H), 1.53 – 1.44 (m, 1H), 1.33 – 1.10 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.4, 77.8, 64.5, 34.5, 32.4, 32.3, 26.0, 24.7, 24.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.2. IR (neat): 2930, 2856, 1380, 1372, 1342, 1140, 1106, 968, 847, 673 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{28}O_3BClNa$ $[M+Na]^+$: 325.1707; found: 325.1712.

Ethyl 4-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (1m)



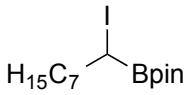
$C_{12}H_{22}BClO_4$
MW: 276.13

From **SI-2** (1.37 g, 6.0 mmol) following **GP3**. The product was purified by vacuum distillation (85 °C, 1×10^{-2} mbar) to afford **1m** as a colorless oil (775 mg, 2.8 mmol, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.47 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.55 (dt, *J* = 8.2, 6.4 Hz, 2H), 2.23 – 2.08 (m, 2H), 1.28 – 1.23 (m,

15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 84.7, 60.6, 32.0, 29.2, 24.8, 24.7, 14.4. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.1. IR (neat): 2979, 2935, 1731, 1372, 1339, 1317, 1138, 968, 845, 671 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{22}O_4BClNa$ $[M+Na]^+$: 299.1186; found: 299.1192.

2.5 Synthesis of α-iodinated pinacolboronic ester 1n[8]

_B_-(1-Iodooctyl)pinacolborane (1n)

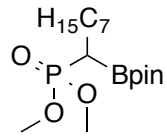


$C_{14}H_{28}BIO_2$
MW: 366.13

A suspension of Schwartz' reagent (2.32 g, 9.0 mmol, 3.0 equiv) in dry CH_2Cl_2 (70 mL, 0.13 M) was stirred at rt under inert atmosphere. A 0.5 M solution of **SI-3** (715 mg, 3.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (6 mL) was then added. The reaction mixture was stirred for 2 h, and became a clear yellow solution. The flask was then protected from the light, and addition of N-iodosuccinimide (810 mg, 3.6 mmol, 1.2 equiv) led to the discharge of the color of the solution. After 20 minutes, the solvent was removed under reduced pressure, *n*-pentane (3×30 mL) was added to extract the reaction mixture, and the corresponding suspension was filtered. The filtrate was washed twice with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* (glassware protected from the light). The corresponding yellow liquid was engaged in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (t, J = 8.2 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.47 – 1.24 (m, 22H), 0.87 (app t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.0, 35.0, 31.9, 31.4, 29.2, 28.9, 24.5, 24.4, 22.8, 14.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.8. IR (neat): 2976, 2957, 2920, 2854, 1378, 1371, 1331, 1140, 844, 671 cm^{-1}. HRMS (EI) calcd. for $C_{14}H_{28}O_2BI$ $[M]^+$: 366.1223; found: 366.1222.

2.6 Synthesis of α-phosphonate pinacolboronic ester 1h[11]

Dimethyl (1-(_B_-pinacolboryl)octyl)phosphonate (1h)



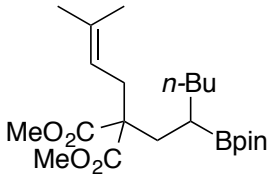
$C_{16}H_{34}BO_5P$
MW: 348.23

Trimethylphosphite (0.68 mL, 5.7 mmol, 2.0 equiv) was added in one portion to freshly prepared **1n** (1.05 g, 2.9 mmol, 1.0 equiv) and the contents were heated at 90 °C for 1 h. The contents were cooled to rt and purified by FCC on silica gel (CH_2Cl_2/MeOH 9:1) to afford **1h** as a yellow oil (0.83 g, 2.4 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (d, J = 10.8 Hz, 3H), 3.72 (d, J = 10.8 Hz, 3H), 1.86 – 1.53 (m, 3H), 1.42 – 1.13 (m, 22H), 0.85 (app t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.1, 52.7 (d, J_{CP} = 6.9 Hz), 52.5 (d, J_{CP} = 6.9 Hz), 31.8, 30.6 (d, J_{CP} = 17.4 Hz), 29.4 (d, J_{CP} = 1.3 Hz), 29.1, 25.1 (d, J_{CP} = 6.3 Hz), 24.8, 24.5, 22.7, 14.2. ^{11}B

NMR (96 MHz, $CDCl_3$) δ 32.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ 35.0. IR (neat): 2977, 2952, 2925, 2853, 1463, 1331, 1246, 1143, 1057, 1028, 967, 848, 810 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{34}O_5BNaP$ $[M+Na]^+$: 371.2117; found: 371.2129.

2.7 Synthesis of cyclization substrate 11

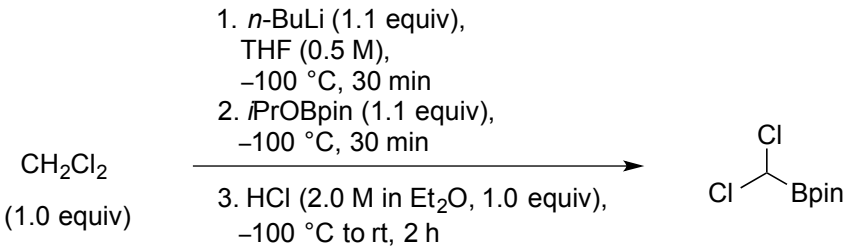
Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl) malonate (11)



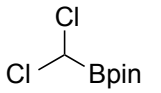
$C_{22}H_{39}BO_6$
MW: 410.36

A modified literature procedure was followed (no added initiator).[12] To a solution of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.19 mL, 2.0 mmol, 1.0 equiv) in TBME (7 mL, 0.3 M) at 0 °C was added slowly *n*-butyllithium (0.88 mL, 2.2 mmol, 2.5 M in hexanes, 1.1 equiv). The solution was stirred at this temperature for 30 min, warmed to rt, and dimethyl 2-bromo-2-(3-methylbut-2-en-1-yl)malonate[12] (1.11 g, 4.0 mmol, 2.0 equiv) was added in one portion. The reaction mixture was heated under reflux at 60 °C for 1.5 h. The cooled reaction mixture was partitioned between TBME (10 mL) and H_2O (10 mL), acidified with 2 M aq. HCl (5 mL), and extracted. The organic phase was extracted again with H_2O (10 mL), and the combined aqueous phases back-extracted with TBME (2 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$, dried with sat. aq. NaCl, and further dried over Na_2SO_4, which was then filtered through a short silica plug and concentrated *in vacuo*. The residue was submitted to FFC on silica gel (2-2-3-4-5-10-20% EtOAc/heptanes) to afford **11** as a clear viscous oil (589 mg, 1.44 mmol, 72%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 – 5.01 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 2.57 (app dABq, $\Delta\delta_{AB}$ = 0.18, J_{AB} = 15.0 Hz, J_A = 8.1 Hz, J_B = 6.7 Hz, 2H), 2.03 (dABq, $\Delta\delta_{AB}$ = 0.30, J_{AB} = 14.3 Hz, J_A = 8.6 Hz, J_B = 3.8 Hz, 2H), 1.67 (d, J = 0.6 Hz, 3H), 1.59 (d, J = 1.5 Hz, 3H), 1.47 – 1.15 (m, 18H, [containing 1.232 (s, 6H), 1.228 (s, 6H)]), 0.92 – 0.78 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 134.9, 118.3, 83.0, 58.2, 52.12, 52.09, 33.7, 32.4, 31.5, 31.0, 26.0, 25.0, 24.7, 22.9, 17.8, 14.0. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.3. IR (neat): 2924, 1732, 1379, 1315, 1213, 1166, 1142, 966 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{40}BO_6$ $[M+H]^+$: 411.2900; found: 411.2899.

2.8 Synthesis of 1p



2-(Dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1p)



$C_7H_{13}BCl_2O_2$
MW: 210.04

To a two-necks, 250 mL round-bottom flask was added THF (100 mL, 0.5 M) and CH_2Cl_2 (3.54 mL, 50.0 mmol, 1.0 equiv) and the solution was cooled to –100 °C using a slurry EtOH/liquid N_2 bath. *n*-Butyllithium (20.1 mL, 50.0 mmol, 1.0 equiv, 2.5 M in *n*-hexane) was added dropwise at this temperature and the resulting suspension was left to stir at –100 °C for 30 minutes. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11.2 mL, 55.0 mmol, 1.1 equiv) was added at once and the reaction mixture was stirred for further 30 minutes at –100 °C. The resulting ate complex was then hydrolyzed at this temperature by addition of dry HCl (25.0 mL, 50.0 mmol, 1.0 equiv, 2.0 M in Et_2O) and the contents were allowed to warm to rt and left to stir for another 2 h. The reaction mixture was diluted with water (50 mL) and the two phases were separated. The aqueous phase was back-extracted with TBME (30 mL), and the collected ethereal phases were washed with aq. sat. NaCl (80 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by vacuum distillation (58 – 60 °C head, 2.4 mbar) to afford **1p** as a colorless oil (4.9 g, 23.3 mmol, 47%). Spectral and physical data were in accordance with the literature.[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 1.33 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.8, 24.5. ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.0.

2.9 Synthesis of DTBHN and MeOBcat

Di-*tert*-butyl hyponitrite (DTBHN)

t-BuON=NO*t*-Bu
$C_8H_{18}N_2O_2$
MW: 174.24

DTBHN was prepared according to a slightly altered literature procedure.[13] A three-necks, 250 mL round-bottom flask equipped with a stirring bar was loaded sodium *trans*-hyponitrite hydrate (8.15 g) which was then dried to constant weight (5.58 g). In another flask, $ZnCl_2$ hydrate (14 g) was melted under stirring *in vacuo* (3x) in order to dry it. From the resulting block of grey solid, pieces with a total weight of 8.6 g (63.1 mmol, 1.2 equiv) were (quickly) transferred into a two-necks, round-bottom flask, dried another 10 min under vacuum, and then suspended in Et_2O (35 mL) first with stirring for 2 h then with sonication for another 20 min until no more pieces of $ZnCl_2$ were visible. To the

dry hyponitrite was added Et_2O (30 mL) and *tert*-butylbromide (47 mL, 418 mmol, 8.0 equiv) and the resulting milky white mixture was cooled to –10 °C (internal temperature) using an ice/NaCl/water bath. Then, the $ZnCl_2$ suspension was transferred into the reaction vessel with the hyponitrite using a cannula (Ø = 1 mm) at a rate that the internal temperature did not exceed –5 °C. After complete addition, the mixture was allowed to reach rt and stirred for another 1.5 h at this temperature. The reaction mixture was filtered and the remaining solid was washed with Et_2O (3×10 mL). The resulting yellow solution was transferred into a separatory funnel and water was added. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and the volatiles were removed under reduced pressure (bath temperature 20 °C, 400 mbar, end to 50 mbar for a short time). The obtained solid was crystallized from *n*-pentane to furnish almost colorless crystals in three crops (all crops were washed with cold *n*-pentane). Recrystallization from *n*-pentane of the combined crops furnished the product as colorless, transparent crystals (3.43 g, 37%). Spectral data is in accordance with the literature. DTBHN was stored for months at 4 °C. Spectral and physical data were in accordance with the literature.[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.3, 27.9.

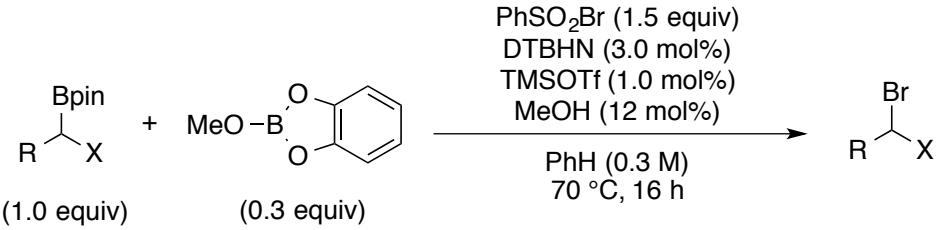
2-Methoxybenzo[*d*][1,3,2]dioxaborole (MeOBcat)

MeOBcat
$C_7H_7BO_3$
MW: 150.05

A one-neck, round-bottom flask was charged with catecholborane (4.0 mL, 37.5 mmol, 1.0 equiv) and benzene (25 mL, 1.5 M). MeOH (1.52 mL, 37.5 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred at rt until no more H_2 evolution was visible (ca. 1 h). The solvent was removed under reduced pressure and the residue was distilled under vacuum (44 °C head, 4×10^{-2} mbar) to afford MeOBcat as a colorless oil (3.2 g, 21.1 mmol, 57%). Spectral and physical data were in accordance with the literature.[14] ^{1}H NMR (300 MHz, C_6D_6) δ 6.93 – 6.88 (m, 2H), 6.77 – 6.71 (m, 2H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 148.6, 122.5, 112.2, 53.1. ^{11}B NMR (96 MHz, C_6D_6) δ 23.4.

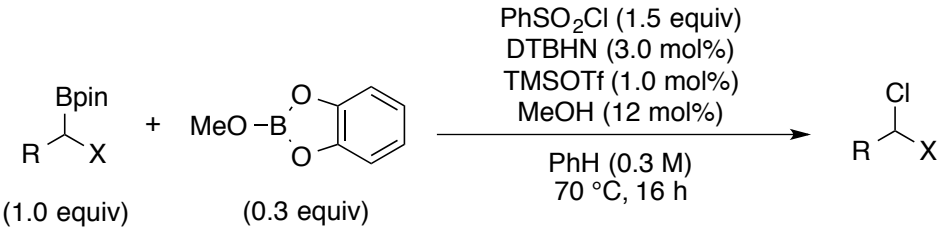
3 General Experimental Procedures for the Deboronative Radical Chain Reactions

3.1 General Procedure 4 (GP4): Bromination of alkyl and α-haloalkyl pinacolboronic esters



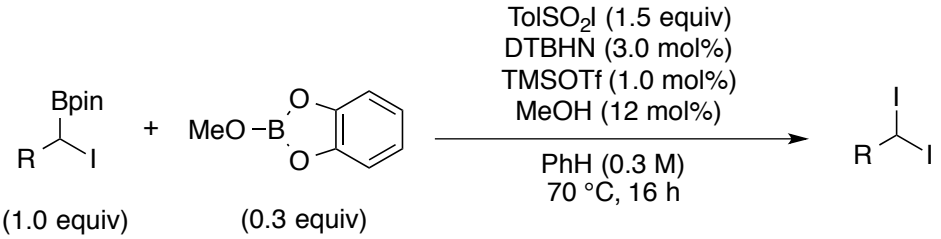
To a two-necks, round-bottom flask equipped with a reflux condenser were added the corresponding alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), benzenesulfonyl bromide (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between *n*-pentane (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with *n*-pentane (20 mL/mmol). The combined organic extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.2 General Procedure 5 (GP5): Chlorination of alkyl and α-haloalkyl pinacolboronic esters



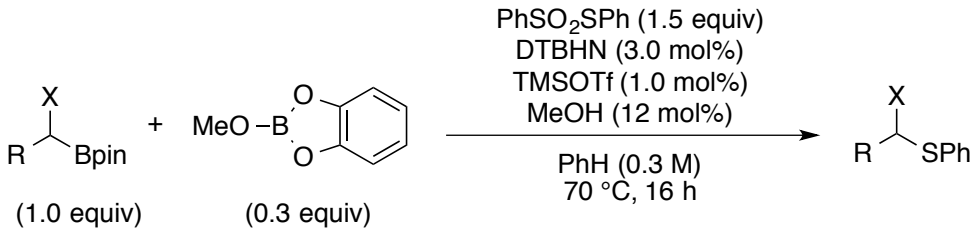
To a two-necks, round-bottom flask equipped with a reflux condenser were added the corresponding alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), benzenesulfonyl chloride (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between *n*-pentane (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with *n*-pentane (20 mL/mmol). The combined organic extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.3 General Procedure 6 (GP6): Iodination of α-iodoalkyl pinacolboronic esters



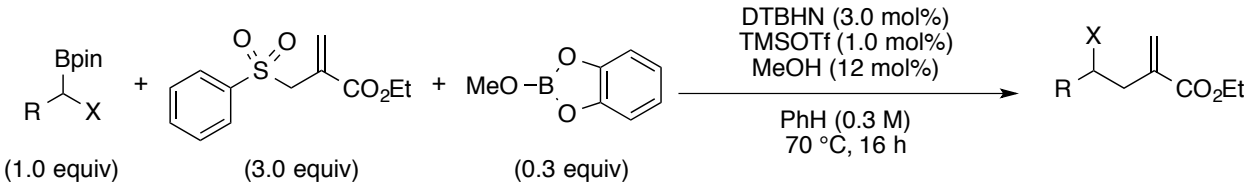
To a two-necks, round-bottom flask equipped with a reflux condenser were added the α-iodooctylpinacolboronic ester (1.0 equiv), *p*-toluenesulfonyl iodide (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between *n*-pentane (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with *n*-pentane (20 mL/mmol). The combined organic extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.4 General Procedure 7 (GP7): Sulfurization of alkyl pinacolboronic esters[15]



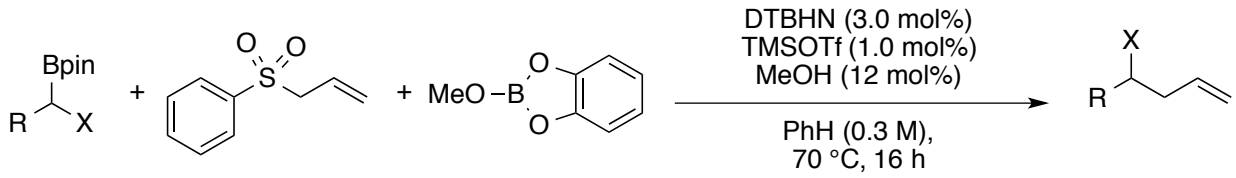
To a two-necks, round-bottom flask equipped with a reflux condenser were added the corresponding alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), *S*-benzyl benzenesulfonothioate (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between TBME (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with TBME (20 mL/mmol). The combined ethereal extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.5 General Procedure 8 (GP8): Allylation of alkyl and α-haloalkyl pinacolboronic esters with ethyl 2-((phenylsulfonyl)-methyl)acrylate[16]



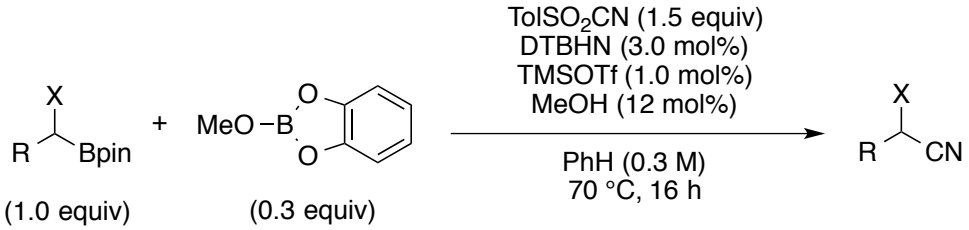
To a two-necks, round-bottom flask equipped with a reflux condenser were added the alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), ethyl 2-((phenylsulfonyl)methyl)acrylate (3.0 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, Then cooled to rt, and partitioned between EtOAc (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with EtOAc (20 mL/mmol). The combined organic extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.6 General Procedure 9 (GP9): Allylation of alkyl and α-haloalkyl pinacolboronic esters with (allylsulfonyl)benzene[16]



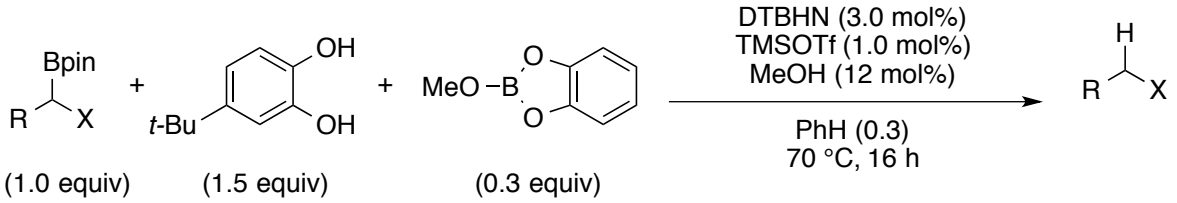
To a two-necks, round-bottom flask equipped with a reflux condenser were added the alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), (allylsulfonyl)benzene (10.0 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between EtOAc (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with EtOAc (20 mL/mmol). The combined organic extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.7 General Procedure 10 (GP10): Cyanation of alkyl and α-haloalkyl pinacolboronic esters[15]



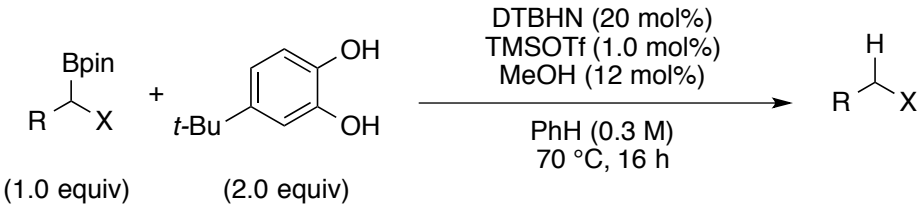
To a two-necks, round-bottom flask equipped with a reflux condenser were added the corresponding alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), p-toluenesulfonyl cyanide (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between TBME (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with TBME (20 mL/mmol). The combined ethereal extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*.

3.8 General Procedure 11 (GP11): Reduction of alkyl and α-haloalkyl pinacolboronic esters with methoxycatecholborane and triflic acid as catalysts[16]



To a two-necks, round-bottom flask equipped with a reflux condenser were added the alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), 4-*tert*-butylcatechol, TBC (1.5 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (3.0 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between TBME (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with TBME (20 mL/mmol). The combined ethereal extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered over celite and the volatiles were removed *in vacuo*.

3.9 General Procedure 12 (GP12): Reduction of α-haloalkyl pinacolboronic esters with triflic acid as catalyst

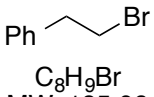


To a two-necks, round-bottom flask equipped with a reflux condenser were added the alkyl or α-haloalkyl pinacolboronic ester (1.0 equiv), 4-*tert*-butylcatechol, TBC (1.5 equiv), PhH (0.3 M), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), MeOH (12 mol%) and DTBHN (20 mol%) in sequence. The contents were heated at 70 °C for 16 h, cooled to rt, and partitioned between TBME (20 mL/mmol) and water (20 mL/mmol). The phases were separated and the aqueous layer was back-extracted with TBME (20 mL/mmol). The combined ethereal extracts were washed with $NaHCO_3$, aq. sat. NaCl, then dried over Na_2SO_4, filtered over celite and the volatiles were removed *in vacuo*.

4 Descriptions of Isolations and Characterizations of Deboronative Radical Chain Reaction Products

4.1 From General Procedure 4: Radical deboronative brominations to furnish 2a–e, 2g–n

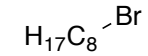
(2-Bromoethyl)benzene (2a)



C_8H_9Br
MW: 185.06

From **1a** (232 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2a** as a colorless oil (139 mg, 0.75 mmol, 75%). This compound was verified by comparison to a commercial sample. CAS Registry Number [103-63-9]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 3.62 (app t, J = 7.6 Hz, 2H), 3.22 (app t, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 128.8, 128.7, 127.0, 39.5, 33.0.

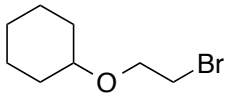
1-Bromooctane (2b)



$C_8H_{17}Br$
MW: 292.19

From **1b** (240 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2b** as a colorless oil (193 mg, 0.66 mmol, 66%). This compound was verified by comparison to a commercial sample. CAS Registry Number [111-85-3]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (t, *J* = 6.9 Hz, 2H), 1.86 (p, *J* = 6.9 Hz, 2H), 1.47 – 1.38 (m, 2H), 1.42 – 1.27 (m, 8H), 0.88 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 33.0, 31.9, 29.2, 28.9, 28.3, 22.8, 14.2.

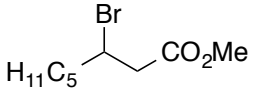
(2-Bromoethoxy)cyclohexane (2c)



$C_8H_{15}BrO$
MW: 207.11

From **1c** (254 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on neutral aluminum oxide (*n*-pentane /EtOAc 99:1) to afford **2c** as a colorless oil (124 mg, 0.60 mmol, 60%). Spectral and physical data were in accordance with the literature.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (t, *J* = 6.5 Hz, 2H), 3.38 (t, *J* = 6.5 Hz, 2H), 3.27 – 3.19 (m, 1H), 1.87– 1.80 (m, 2H), 1.71 – 1.64 (m, 2H), 1.50 – 1.43 (m, 1H), 1.30 – 1.10 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$) δ 78.3, 68.1, 32.4, 31.2, 25.9, 24.2. IR (neat): 2930, 2855, 1449, 1362, 1276, 1115, 1089, 1023, 966, 887, 862, 844, 676 cm^{-1}. HRMS (EI) calcd. for $C_8H_{15}{}^{79}BrO$ $[M]^+$: 206.0301; found: 206.0298; calculated for $C_8H_{15}{}^{81}BrO$ $[M]^+$: 208.0280; found: 208.0279.

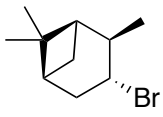
Methyl 3-bromooctanoate (2d)



$C_9H_{17}BrO_2$
MW: 236.04

From **1d** (284 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (heptanes/EtOAc 98:2) to afford **2d** as a colorless oil (191 mg, 0.76 mmol, 76%). Spectral and physical data were in accordance with the literature.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (pj, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 2.90 (d, *J* = 7.1 Hz, 2H), 1.86 – 1.79 (m, 2H), 1.62 – 1.22 (m, 6H), 0.90 (app t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 52.1, 50.2, 44.3, 38.8, 31.1, 27.3, 22.6, 14.1. IR (neat): 2954, 2930, 2859, 1739, 1436, 1374, 1270, 1212, 1151, 1008, 991, 928, 890, 845, 726, 714 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{17}O_2BrNa$ $[M+Na]^+$: 259.0304; found: 259.0300.

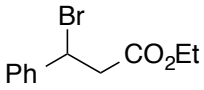
(1*R*,2*R*,3*R*,5*S*)-3-Bromo-2,6,6-trimethylbicyclo[3.1.1]heptane (2e)



$C_{10}H_{17}Br$
MW: 216.05

From **1e** (264 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2e** as a colorless liquid (122 mg, 0.56 mmol, 56%). Spectral and physical data were in accordance with the literature.[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (dt, *J* = 9.7, 7.0 Hz, 1H), 2.72 (ddt, *J* = 13.7, 9.8, 3.0 Hz, 1H), 2.59 (pd, *J* = 7.2, 1.7 Hz, 1H), 2.52 – 2.42 (m, 2H), 1.96 (dtd, *J* = 6.0, 3.4, 1.8 Hz, 1H), 1.87 (td, *J* = 6.0, 1.8 Hz, 1H), 1.22 (d, *J* = 8.5 Hz, 1H), 1.21 (s, 3H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.9, 49.6, 49.5, 43.5, 41.0, 38.6, 35.4, 28.1, 24.0, 20.4.

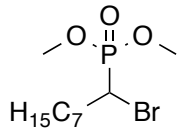
Ethyl 3-bromo-3-phenylpropanoate (2g)



$C_{11}H_{13}BrO_2$
MW: 257.13

From **1g** (304 mg, 1.0 mmol), following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2g** as a colorless oil (193 mg, 0.75 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 5.32 (dd, *J* = 8.9, 6.3 Hz, 1H), 4.06 (qd, *J* = 7.1, 1.7 Hz, 2H), 3.25 (dd, *J* = 16.1, 8.9 Hz, 1H), 3.10 (dd, *J* = 16.1, 6.3 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 140.9, 128.9, 128.8, 127.2, 61.1, 48.1, 44.9, 14.2. IR (neat): 2980, 1732, 1455, 1376, 1266, 1188, 1142, 1018, 936, 869, 763, 693, 627, 614, 574, 517 cm^{-1}. HRMS (EI positive ion) calcd. for $C_{11}H_{13}{}^{79}BrO_2$ $[M]^+$: 256.0093; found: 256.0093.

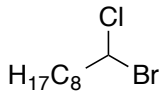
Dimethyl (1-bromooctyl)phosphonate (2h)



$C_{10}H_{22}BrO_3P$
MW: 301.16

From **1h** (348 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (heptanes/EtOAc 1:1) to afford **2h** as a yellowish oil (174 mg, 0.58 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 10.7, 7.8 Hz, 6H), 3.87 – 3.75 (m, 1H), 2.15 – 1.99 (m, 1H), 1.98 – 1.77 (m, 1H), 1.73 – 1.58 (m, 1H), 1.48 – 1.19 (m, 9H), 0.84 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.5 (d, J_{CP} = 7.1 Hz), 54.0 (d, J_{CP} = 7.1 Hz), 41.7 (d, J_{CP} = 158.6 Hz), 32.4 (d, J_{CP} = 1.9 Hz), 31.8, 29.1, 28.7, 27.7 (d, J_{CP} = 12.4 Hz), 22.7, 14.2. ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.8. IR (neat): 2925, 2854, 1460, 1255, 1183, 1024, 823, 751, 595, 547 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{23}O_3BrP$ $[M+H]^+$: 301.0563; found: 301.0561.

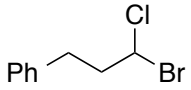
1-Bromo-1-chlorononane (2i)



$C_9H_{18}BrCl$
MW: 241.60

From **1i** (115 mg, 0.40 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2i** as a colorless oil (79 mg, 0.33 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (t, *J* = 6.2 Hz, 1H), 2.32 – 2.25 (m, 2H), 1.60 – 1.48 (m, 2H), 1.37 – 1.25 (m, 10H), 0.89 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.1, 44.8, 31.9, 29.5, 29.3, 28.6, 27.2, 22.8, 14.2. IR (neat): 2952, 2924, 2854, 1458, 1434, 1376, 1362, 1340, 1301, 1191, 1031, 746, 684 cm^{-1}. HRMS (EI) calcd. for $C_9H_{17}Br$ $[M\text{-}HCl]^+$: 204.0508; found: 204.0510.

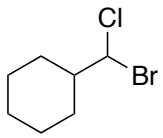
(3-Bromo-3-chloropropyl)benzene (2j)



$C_9H_{10}BrCl$
MW: 231.97

From **1j** (281 mg, 1.0 mmol), following **GP4**. The product was purified by FCC on silica gel (heptanes 100%) to afford **2j** as a colorless oil (155 mg, 0.67 mmol, 67%). Spectral and physical data were in accordance with the literature.[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.12 (m, 5H), 5.59 (t, *J* = 6.2 Hz, 1H), 2.82 – 2.77 (m, 2H), 2.56 – 2.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 128.9, 128.7, 126.7, 60.1, 46.1, 33.2.

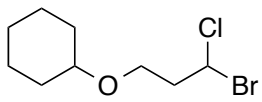
(Bromochloromethyl)cyclohexane (2k)



$C_7H_{12}BrCl$
MW: 209.98

From **1k** (259 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2k** as a colorless oil (176 mg, 0.84 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 3.9 Hz, 1H), 1.97 – 1.80 (m, 5H), 1.70 – 1.67 (m, 1H), 1.31 – 1.13 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.8, 49.1, 29.5, 29.2, 26.1, 25.73, 25.70. IR (neat): 2928, 2854, 1450, 1296, 1235, 1186, 1170, 959, 885, 790, 736, 692, 656, 630, 602 cm^{-1}. HRMS (EI) calcd. for $C_7H_{12}Br$ $[M\text{-}Cl]^+$: 175.0117; found: 175.0120.

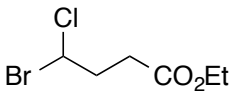
(3-Bromo-3-chloropropoxy)cyclohexane (2l)



$C_9H_{16}BrClO$
MW: 254.01

From **1l** (303 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (heptanes 100%) to afford **2l** as a colorless oil (109 mg, 0.43 mmol, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (t, *J* = 6.6 Hz, 1H), 3.61 – 3.55 (m, 2H), 3.27 – 3.17 (m, 1H), 2.54 – 2.49 (m, 2H), 1.86 – 1.71 (m, 4H), 1.61 – 1.46 (m, 1H), 1.29 – 1.20 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.9, 64.4, 58.6, 45.4, 32.22, 32.20, 25.9, 24.1. IR (neat): 2929, 2856, 1448, 1363, 1286, 1239, 1175, 1106, 969, 747.8, 707, 632 cm^{-1}. HRMS (EI) calcd. for $C_9H_{16}OBrCl$ $[M]^+$: 254.0068; found: 254.0071.

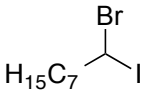
Ethyl 4-bromo-4-chlorobutanoate (2m)



$C_6H_{10}BrClO_2$
MW: 227.96

From **1m** (277 mg, 1.0 mmol) following **GP4**. The product was purified by FCC on silica gel (heptanes/EtOAc 98:2) to afford **2m** as a colorless oil (109 mg, 0.48 mmol, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 – 5.89 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.58 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 61.0, 59.5, 39.4, 31.5, 14.3. IR (neat): 2982, 2937, 1728, 1432, 1375, 1313, 1182, 1095, 1029, 852, 798, 752, 676 cm^{-1}. HRMS (ESI) calcd. for $C_6H_{11}O_2BrCl$ $[M+H]^+$: 228.9626; found: 228.9628.

1-Bromo-1-iodooctane (2n)

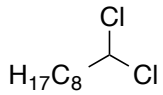


$C_8H_{16}BrI$
MW: 317.95

From **1n** (170 mg, 0.46 mmol) and benzenesulfonyl bromide (154 mg, 0.70 mmol) following **GP4**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **2n** as a light-yellow oil (127 mg, 0.40 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (t, *J* = 6.4 Hz, 1H), 2.45 – 2.30 (m, 2H), 1.53 – 1.45 (m, 2H), 1.35 – 1.26 (m, 10H), 0.89 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 47.3, 31.8, 30.0, 29.2, 28.1, 22.7, 14.2, 13.0. IR (neat): 2953, 2923, 2853, 1457, 1429, 1377, 1129, 912, 827, 722, 661, 630 cm^{-1}. HRMS (EI) calcd. for $C_8H_{16}{}^{79}BrI$ [M]+: 319.9475; found: 319.9453.

4.2 From General Procedure 5: Radical deboronative chlorinations to furnish 3i–m

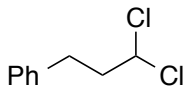
1,1-Dichlorononane (3i)



$C_9H_{18}Cl_2$
MW: 196.08

From **1i** (289 mg, 1.0 mmol) following **GP5**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **3i** as a colorless oil (144 mg, 0.73 mmol, 73%). Spectral and physical data were in accordance with the literature.[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (t, *J* = 6.1 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.56 – 1.51 (m, 2H), 1.30 – 1.26 (m, 10H), 0.89 (app t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.7, 43.7, 31.8, 29.3, 29.1, 28.6, 26.0, 22.7, 14.1.

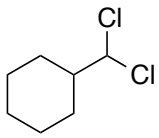
(3,3-Dichloropropyl)benzene (3j)



$C_9H_{10}Cl_2$
MW: 196.08

From **1j** (281 mg, 1.0 mmol) following **GP5**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **3j**[†] as a colorless oil (124 mg, 0.66 mmol, 66%). Spectral and physical data were in accordance with the literature.[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.11 (m, 5H), 5.58 (t, *J* = 6.1 Hz, 1H), 2.82 – 2.78 (m, 2H), 2.46 – 2.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 128.8, 128.6, 126.7, 72.9, 45.1, 32.3. [†]contaminated with 3-chloropropylbenzene.

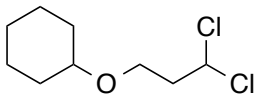
Dichloromethylcyclohexane (3k)



$C_7H_{12}Cl_2$
MW: 166.03

From **1k** (146 mg, 0.57 mmol) following **GP5**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford as a colorless oil **3k** (44 mg, 0.26 mmol, 47%). Spectral and physical data were in accordance with the literature.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, *J* = 3.9 Hz, 1H), 1.96 – 1.81 (m, 5H), 1.72 – 1.67 (m, 2H), 1.30 – 1.17 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.8, 48.5, 28.4, 25.9, 25.6.

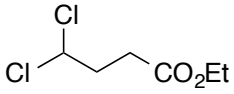
3,3-Dichloropropoxycyclohexane (3l)



$C_9H_{16}Cl_2O$
MW: 210.06

From **1l** (142 mg, 0.47 mmol) following **GP5**. The product was purified by two FCC (1st FCC: silica gel (*n*-pentane/ CH_2Cl_2 8:2); 2nd FCC: neutral aluminium oxide (*n*-pentane 100%)) to afford **3l** as a colorless oil (55 mg, 0.26 mmol, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (t, *J* = 6.5 Hz, 1H), 3.61 (t, *J* = 5.6 Hz, 2H), 3.23 (tt, *J* = 8.8, 3.9 Hz, 1H), 2.45 – 2.39 (m, 2H), 1.90 – 1.83 (m, 2H), 1.73 – 1.71 (m, 2H), 1.53 – 1.48 (m, 1H), 1.33 – 1.17 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.7, 71.4, 63.6, 44.3, 32.1, 25.8, 24.0. HRMS (EI) calcd. for $C_9H_{16}Cl_2O$ $[M]^+$: 210.0569; found: 210.0573.

Ethyl 4,4-dichlorobutanoate (3m)

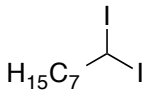


$C_6H_{10}Cl_2O_2$
MW: 184.01

From **1m** (277 mg, 1.0 mmol) following **GP5**. The product was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 95:5 to 1:1) to afford **3m** as a colorless oil (79 mg, 0.43 mmol, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (t, *J* = 5.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.66 – 2.46 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 72.5, 61.0, 38.5, 30.5, 14.3. IR (neat): 2982, 1729, 1440,1376, 1317, 1294, 1253, 1216, 1185, 1164, 1094, 1030, 887, 852, 802, 756, 676, 645 cm^{-1}. HRMS (ESI) calcd. for $C_6H_{11}O_2Cl_2$ $[M+H]^+$: 185.0131; found: 185.0131.

4.3 From General Procedure 6: Radical deboronative iodination to furnish 4n

1,1-Diiodooctane (4n)

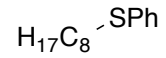


$C_8H_{16}I_2$
MW: 365.93

From **1n** (170 mg, 0.46 mmol) following **GP6**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **4n** as a light pink oil (147 mg, 0.40 mmol, 87%). Spectral and physical data were in accordance with the literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (t, *J* = 6.5 Hz, 1H), 2.35 (dd, *J* = 14.5, 6.5 Hz, 2H), 1.43 – 1.28 (m, 10H), 0.91 – 0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.4, 31.8, 31.7, 29.0, 27.6, 22.6, 14.1, –25.2.

4.4 From General Procedure 7: Radical deboronative sulfurizations to furnish 5b, 5e–f

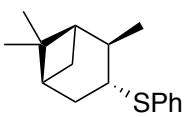
Octyl(phenyl)sulfane (5b)



$C_{14}H_{22}S$
MW: 222.14

From **1b** (240 mg, 1.0 mmol) following **GP7**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **5b** as a colorless liquid (177 mg, 0.80 mmol, 80%). Spectral and physical data were in accordance with the literature.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 5H), 2.92 (app t, *J* = 7.2 Hz, 2H), 1.68 (p, *J* = 7.2 Hz, 2H), 1.45 – 1.38 (m, 2H), 1.37 – 1.27 (m, 8H), 0.91 (app t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 129.0, 128.9, 125.8, 33.7, 31.9, 29.3, 29.31, 29.29, 29.0, 22.8, 14.2.

Phenyl((1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)sulfane (5e)



$C_{16}H_{22}S$
MW: 246.14

From **1e** (264 mg, 1.0 mmol) following **GP7**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **5e** as a colorless oil (113 mg, 0.46 mmol, 46%). Spectral and physical data were in accordance with the literature.[15] $[\alpha]_D^{20}$ – 77.6° (*c* 1.00, $CHCl_3$ (HPLC grade, stabilized on EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 2H), 7.37 – 7.24 (m, 3H), 3.45 (ddd, *J* = 9.8, 7.2, 5.8 Hz, 1H), 2.57 (dddd, *J* = 13.2, 9.8, 3.2, 2.3 Hz, 1H), 2.38 (dtd, J = 9.5, 6.2, 2.2 Hz, 1H), 2.15 (dddd, *J* = 14.6, 8.1, 6.5, 2.3 Hz, 2H), 1.98 (tt, *J* = 5.9, 3.0 Hz, 1H), 1.89 (td, *J* = 5.9, 2.0 Hz, 1H), 1.26 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 1.04 (d, *J* = 9.8 Hz, 1H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 136.8, 131.7, 128.9, 126.6, 48.1, 45.3, 44.5, 42.1, 38.8, 37.8, 33.5, 27.9, 23.5, 21.6.

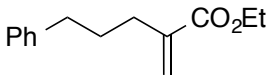
Bicyclo[2.2.1]heptan-2-yl(phenyl)sulfane (5f)

$C_{13}H_{16}S$
MW: 204.10

From **1f** (222 mg, 1.0 mmol) following **GP7**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **5f** as a colorless liquid (183 mg, 0.90 mmol, 90%). Spectral and physical data were in accordance with the literature.[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 4H), 7.11 – 7.05 (m, 1H), 3.12 (ddd, *J* = 8.3, 4.5, 1.6 Hz, 1H), 2.28 – 2.17 (m, 2H), 1.73 (ddd, *J* = 13.0, 8.3, 2.3 Hz, 1H), 1.62 (ddt, *J* = 10.1, 3.9, 2.3 Hz, 1H), 1.57 – 1.43 (m, 2H), 1.35 (dtd, *J* = 12.9, 4.4, 2.9 Hz, 1H), 1.25 – 1.04 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 129.1, 128.9, 125.7, 48.3, 42.5, 38.7, 36.6, 35.7, 29.1, 28.8.

4.5 From General Procedure 8: Radical deboronative allylations to furnish 6a–d, 6g–m and 6o–p

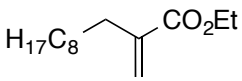
Ethyl 5-(cyclohexyloxy)-2-methylenepentanoate (6a)



$C_{14}H_{18}O_2$
MW: 218.30

From **1a** (232 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on silica gel (heptanes/Et_2O 99:1) to afford **6a** as a colorless oil (120 mg, 0.55 mmol, 55%). Spectral and physical data were in accordance with the literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.12 (m, 5H), 6.14 (d, *J* = 1.1 Hz, 1H), 5.51 (d, *J* = 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.72 – 2.58 (m, 2H), 2.39 – 2.25 (m, 2H), 1.87 – 1.73 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 142.3, 140.9, 128.6, 128.5 , 125.9, 124.7, 60.7, 35.6, 31.7, 30.2, 14.4. IR (neat): 3107, 3085, 3063, 3027, 2980, 2932, 2861, 1713, 1630, 1453, 1368, 1289, 1177, 1129, 941, 818, 750, 743, 698 cm^{-1}. HRMS (EI) calcd. for $C_{14}H_{18}O_2$ $[M]^+$: 218.1301; found: 218.1305.

Ethyl 2-methyleneundecanoate (6b)

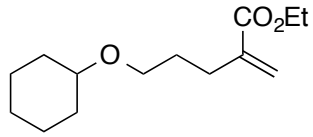


$C_{14}H_{26}O_2$
MW: 226.36

From **1b** (0.240 g, 1.0 mmol) following **GP8**. The product was purified by FCC on silica gel (*n*-pentane/EtOAc 99:1) to afford **6b** as a colorless oil (120 mg, 0.53 mmol, 53%). Spectral and physical data were in accordance with the literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 1.3 Hz, 1H), 5.47 (d, *J* = 1.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.29 – 2.24 (m, 2H), 1.48 –

1.18 (m, 17H), 0.85 (app t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 141.3, 124.1, 60.6, 31.99, 31.96, 29.6, 29.5, 29.4, 29.3, 28.5, 22.8, 14.3, 14.2. IR (neat): 2924, 2854, 1717, 1631, 1464, 1407, 1368, 1298, 1260, 1239, 1176, 1145, 1097, 1028, 938, 817 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{27}O_2$ $[M+H]^+$: 227.2006; found: 227.2008.

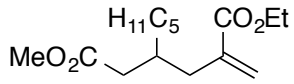
Ethyl 5-(cyclohexyloxy)-2-methylenepentanoate (6c)



$C_{14}H_{24}O_3$
MW: 240.34

From **1c** (254 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **6c** as a colorless oil (108 mg, 0.45 mmol, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 0.7 Hz, 1H), 5.53 (d, J = 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.45 (t, J = 6.5 Hz, 2H), 3.25 – 3.10 (m, 1H), 2.37 (app t, J = 7.6 Hz, 2H), 1.99 – 1.82 (m, 2H), 1.79 – 1.65 (m, 4H), 1.54 – 1.49 (m, 1H), 1.33 – 1.15 (m, 5H), 1.26 (app t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 140.6, 124.7, 77.6, 67.1, 60.7, 32.5, 28.9, 28.7, 26.0, 24.4, 14.4. IR (neat): 2930, 2855, 1715, 1630, 1448, 1365, 1198, 1143, 1106, 1092, 1025, 940, 817, 687 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{24}O_3Na$ $[M+Na]^+$: 263.1618; found: 263.1612.

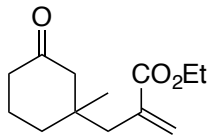
1-Ethyl 6-methyl 2-methylene-4-pentylhexanedioate (6d)



$C_{15}H_{26}O_4$
MW: 270.37

From **1d** (284 mg, 1.0 mmol) following **GP8**. The product was purified by two FCC (1st FCC: silica gel (heptanes/EtOAc 95:5); 2nd FCC: neutral aluminium oxide (heptanes/EtOAc 98:2)) to afford **6d** as a colorless oil (87 mg, 0.32 mmol, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 1.5 Hz, 1H), 5.53 (d, J = 1.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.64 (s, 3H), 2.48 – 2.42 (m, 1H), 2.34 – 2.06 (m, 4H), 1.37 – 1.26 (m, 11H), 0.88 (app t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 167.2, 139.3, 126.5, 60.8, 51.5, 38.6, 36.9, 34.21, 34.16, 32.1, 26.3, 22.7, 14.3, 14.2. IR (neat): 2953, 2927, 2857, 1737, 1715, 1436, 1367, 1297, 1256, 1184, 1161, 1144, 1027, 944, 818, 726, 687 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{26}O_4Na$ $[M+Na]^+$: 293.1728; found: 293.1726.

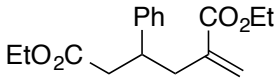
Ethyl 2-((1-methyl-3-oxocyclohexyl)methyl)acrylate (6o)



$C_{13}H_{20}O_3$
MW: 224.30

From **1o** (238 mg, 1.0 mmol) following **GP8**. The product was purified by two FCC (1st FCC: silica gel (toluene/EtOAc 95:5); 2nd FCC: neutral aluminium oxide (toluene/EtOAc 98:2)) to afford **6o** as a colorless oil (72 mg, 0.32 mmol, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, J = 1.6 Hz, 1H), 5.57 – 5.37 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.42 – 2.13 (m, 5H), 2.04 – 1.72 (m, 3H), 1.65 – 1.44 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 167.8, 137.3, 128.5, 60.9, 52.8, 43.1, 41.0, 39.5, 35.9, 24.3, 22.1, 14.2. IR (neat): 2957, 2875, 1710, 1625, 1311, 1290, 1189, 1175, 1026, 950, 818, 505 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{20}O_3Na$ $[M+Na]^+$: 247.1305; found: 247.1308.

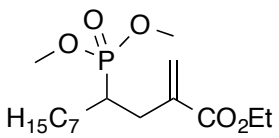
Diethyl 2-methylene-4-phenylhexanedioate (6g)



$C_{17}H_{22}O_4$
MW: 290.36

From **1g** (304 mg, 1.0 mmol) following **GP8**. The product was purified by two FCC (1st FCC: silica gel (toluene/Et_2O 97:3); 2nd FCC: neutral aluminium oxide (toluene/Et_2O 97:3)) to afford **6g** as a colorless oil (160 mg, 0.55 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.08 (m, 5H), 6.02 (d, J = 1.4 Hz, 1H), 5.30 (d, J = 1.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.01 – 3.84 (m, 2H), 3.41 – 3.24 (m, 1H), 2.67 – 2.44 (m, 4H), 1.20 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 166.9, 143.2, 138.4, 128.4, 127.6, 127.0, 126.7, 60.7, 60.3, 41.1, 40.7, 38.9, 14.2, 14.1. IR (neat): 2980, 1713, 1369, 1299, 1262, 1158, 1133, 1028, 946, 817, 762, 699, 533 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591; found: 291.1587.

Ethyl 4-(dimethoxyphosphoryl)-2-methyleneundecanoate (6h)

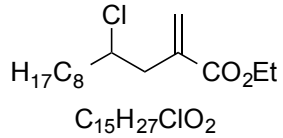


$C_{16}H_{31}O_5P$
MW: 334.39

From **1h** (348 mg, 1.0 mmol) following **GP8** (48 h reaction time). The product was purified by FCC on silica gel (heptanes/EtOAc 1:1) to afford **6h** as a yellowish oil (124 mg, 0.37 mmol, 37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.59 (d, J = 1.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 10.6 Hz, 3H), 3.69 (d, J = 10.6 Hz, 3H), 2.71 – 2.63 (m, 1H), 2.46 – 2.33 (m, 1H), 2.20 – 2.05 (m, 1H), 1.70 – 1.57 (m, 1H), 1.50 – 1.35 (m, 2H), 1.28 (t, J = 7.3 Hz, 3H), 1.24 – 1.21 (m, 9H), 0.84 (app t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 138.2 (d, J_{CP} = 12.1 Hz), 127.2, 60.8, 52.4 (d, J_{CP} = 6.9 Hz), 52.3 (d, J_{CP} = 6.9 Hz), 34.3 (d, J_{CP} = 138.6 Hz), 32.0 (d, J_{CP} = 2.7 Hz), 31.9, 29.7, 29.1, 28.2 (d, J_{CP} = 3.5 Hz), 27.6 (d, J_{CP} = 7.5 Hz), 22.7, 14.3, 14.2. ^{31}P NMR (121 MHz, $CDCl_3$) δ 36.1. IR

(neat): 3468, 2952, 2925, 2854, 1713, 1463, 1242, 1184, 1144, 1055, 1025, 946, 817, 554 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{32}O_5P$ $[M+H]^+$: 335.1982; found: 335.1970.

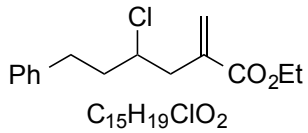
Ethyl 4-chloro-2-methylene-dodecanoate (6i)



$C_{15}H_{27}ClO_2$
MW: 274.17

From **1i** (289 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **6i** as a light-yellow oil (215 mg, 0.78 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, *J* = 1.2 Hz, 1H), 5.70 – 5.68 (m, 1H), 4.22 (qd, *J* = 7.2, 0.3 Hz, 2H), 4.11 (tt, *J* = 9.0, 4.6 Hz, 1H), 2.83 (ddd, *J* = 14.4, 4.5, 0.9 Hz, 1H), 2.57 (dd, *J* = 14.6, 8.9 Hz, 1H), 1.85 – 1.63 (m, 2H), 1.62 – 1.38 (m, 2H), 1.36 – 1.14 (m, 13H), 0.88 (app t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 136.8, 128.2, 61.6, 60.9, 41.5, 38.4, 31.9, 29.5, 29.2, 29.1, 26.4, 22.7, 14.2, 14.1. IR (neat): 2925, 2854, 1714, 1631, 1191, 1146, 1026, 951, 816, 686 cm^{-1}. HRMS (EI) calcd. for $C_{15}H_{27}ClO_2$ [M]+: 274.1697; found: 274.1694.

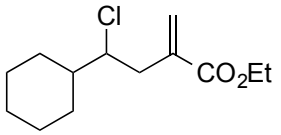
Ethyl 4-chloro-2-methylene-6-phenyl-hexanoate (6j)



$C_{15}H_{19}ClO_2$
MW: 266.11

From **1j** (218 mg, 0.77 mmol) following **GP8**. The product was purified by FCC on neutral aluminium oxide (*n*-pentane 100%) to afford **6j** as a colorless liquid (146 mg, 0.55 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 6.30 (d, *J* = 1.2 Hz, 1H), 5.67 (d, *J* = 1.1 Hz, 1H), 4.18 (qd, *J* = 7.1, 0.9 Hz, 2H), 4.09 (dt, *J* = 9.0, 4.5 Hz, 1H), 3.00 – 2.59 (m, 4H), 2.18 – 1.92 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 141.1, 136.7, 128.63, 128.60, 128.5, 126.2, 61.0, 60.8, 41.6, 40.1, 32.8, 14.3. IR (neat): 2980, 2928, 1712, 1632, 1301, 1193, 1139, 951, 749, 700 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{19}O_2ClNa$ $[M+Na]^+$: 289.0961; found: 289.0966.

Ethyl 4-chloro-4-cyclohexyl-2-methylene-butanoate (6k)

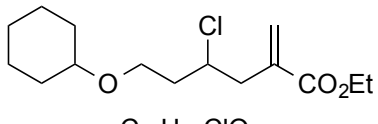


$C_{13}H_{21}ClO_2$
MW: 244.12

From **1k** (259 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on silica gel (*n*-pentane 100% to *n*-pentane/Et_2O 1:1) to afford **6k**† as a colorless liquid (160 mg, 0.65 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, *J* = 1.5 Hz, 1H), 5.69 – 5.67 (m, 1H), 4.21 (qd, *J* = 7.1, 0.5 Hz, 2H), 4.01 (dt, *J* = 10.0, 3.8 Hz, 1H), 2.74 (ABX, J_{AB} = 14.5 Hz, J_{AX} = 3.3 Hz, J_{BX} = 10.0 Hz, $\Delta\nu_{AB}$ = 113 Hz, 2H), 1.84 – 1.61 (m, 6H), 1.33 – 1.12 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 137.2, 128.2, 67.1, 60.9,

44.3, 38.6, 30.2, 28.0, 26.4, 26.3, 26.1, 14.3. HRMS (ESI) calcd. for $C_{13}H_{21}O_2ClNa$ $[M+Na]^+$: 267.1123; found: 267.1122. †contaminated with ethyl 2-(cyclohexylmethyl)acrylate in 97:3 ^1H NMR ratio.

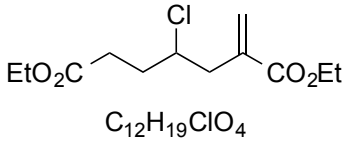
Ethyl 4-chloro-6-(cyclohexoxy)-2-methylene-hexanoate (6l)



$C_{15}H_{25}ClO_3$
MW: 288.15

From **1l** (303 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on neutral aluminium oxide (*n*-pentane 100%) to afford **6l**† as a colorless liquid (172 mg, 0.60 mmol, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J = 1.1 Hz, 1H), 5.69 (d, J = 1.1 Hz, 1H), 4.34 – 4.27 (m, 1H), 4.25 – 4.17 (m, 2H), 3.63 (ddd, J = 8.0, 5.1, 2.6 Hz, 2H), 3.25 – 4.27 (mk, 1H), 2.74 (ABX, J_{AB} = 14.5 Hz, J_{AX} = 4.9 Hz, J_{BX} = 8.9 Hz, $\Delta\nu_{AB}$ = 47 Hz, 2H), 2.07 (dddd, J = 14.4, 7.7, 6.7, 3.7 Hz, 1H), 1.91 – 1.69 (m, 5H), 1.54 – 1.48 (m, 1H), 1.33 – 1.19 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.8, 128.4, 77.8, 64.6, 61.0, 58.7, 41.5, 38.9, 32.5, 32.3, 26.0, 24.24, 24.22, 14.3. IR (neat): 2930, 2856, 1713, 1631, 1192, 1142, 1109, 947, 816, 691 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{25}O_3ClNa$ $[M+Na]^+$: 311.1383; found: 311.1384. †contaminated with ethyl 5-(cyclohexyloxy)-2-methylenepentanoate in 10:1 ^1H NMR ratio.

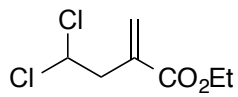
Diethyl 4-chloro-2-methylene-heptanedioate (6m)



$C_{12}H_{19}ClO_4$
MW: 262.10

From **1m** (166 mg, 0.6 mmol) following **GP8**. The product was purified by two FCC (1st FCC: silica gel (*n*-pentane/Et_2O 95:5); 2nd FCC: neutral aluminium oxide (*n*-pentane/Et_2O 95:5)) to afford **6m**† as a colorless oil (70 mg, 0.27 mmol, 44%). **NMR yields:** from ethyl 4-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (111 mg, 0.4 mmol) following **GP8** to afford **6m** in 63% NMR yield. ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, J = 1.1 Hz, 1H), 5.70 (d, J = 1.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.16 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.82 (ddd, J = 14.3, 4.9, 0.8 Hz, 1H), 2.68 – 2.44 (m, 3H), 2.18 (dddd, J = 14.5, 8.9, 6.8, 3.5 Hz, 1H), 1.93 (dtd, J = 14.6, 8.8, 5.7 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).. ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 166.7, 136.5, 128.7, 61.1, 60.7, 60.6, 41.5, 33.3, 31.4, 14.34, 14.30. IR (neat): 2985, 2937, 1714, 1628, 1306, 1188, 1142, 1083, 687, 656 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{19}O_4ClNa$ $[M+Na]^+$: 285.0870; found: 285.0864. †contaminated with diethyl 2-methylenehexanedioate in 92:8 ^1H NMR ratio.

Ethyl 4,4-dichloro-2-methylenebutanoate (6p)

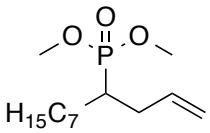


$C_7H_{10}Cl_2O_2$
MW: 196.01

From **1p** (210 mg, 1.0 mmol) following **GP8**. The product was purified by FCC on neutral aluminium oxide (pentane/CH_2Cl_2 9:1) to afford **6p** as a 5:1 mixture of rotamers as a colorless oil (160 mg, 0.82 mmol, 82%). *Mixture of rotamers:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (dt, *J* = 9.7, 0.9 Hz, 0.2H), 6.39 (d, *J* = 0.9 Hz, 1H), 6.00 (t, *J* = 6.6 Hz, 1H), 5.93 (t, *J* = 6.6 Hz, 0.2H), 5.80 (d, *J* = 1.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 0.4H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.18 (dd, *J* = 6.6, 0.9 Hz, 2H), 3.16 (dd, *J* = 6.6, 0.9 Hz, 0.4H), 1.36 (t, *J* = 7.1 Hz, 0.6H), 1.32 (t, *J* = 7.1 Hz, 3H). *Major rotamer:* ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 134.6, 130.5, 71.1, 61.2, 46.8, 14.2. IR (neat): 1709, 1633, 1194, 1142, 1022, 959, 769, 684 cm^{-1}. HRMS (ESI) calcd. for $C_7H_{11}O_2Cl_2$ $[M+Na]^+$: 197.0131; found: 197.0132.

4.6 From General Procedure 9: Radical deboronative allylations to furnish 7h, 7j–m

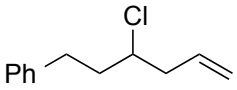
Dimethyl (undec-1-en-4-yl)phosphonate (7h)



$C_{13}H_{27}O_3P$
MW: 262.33

From **1h** (348 mg, 1.0 mmol) following **GP9** (48 h reaction time). The product was purified by FCC on neutral aluminium oxide (heptanes/EtOAc 1:1) to afford **7h** as a yellowish oil (105 mg, 0.4 mmol, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.22 – 4.92 (m, 2H), 3.71 (d, *J* = 10.5 Hz, 3H), 3.70 (d, *J* = 10.5 Hz, 3H), 2.51 – 2.35 (m, 1H), 2.31 – 2.15 (m, 1H), 1.88 – 1.72 (m, 1H), 1.70 – 1.15 (m, 12H), 0.84 (app t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9 (d, J_{CP} = 10.7 Hz), 116.9, 52.5 (d, J_{CP} = 6.9 Hz), 52.4 (d, J_{CP} = 6.9 Hz), 35.6 (d, J_{CP} = 139.2 Hz), 32.7 (d, J_{CP} = 3.4 Hz), 31.9, 29.6, 29.1, 27.7 (d, J_{CP} = 3.4 Hz), 27.5 (d, J_{CP} = 9.1 Hz), 22.7, 14.2. ^{31}P NMR (121 MHz, $CDCl_3$) δ 36.5. IR (neat): 2952, 2925, 2853, 1463, 1242, 1182, 1056, 1025, 912, 816, 557 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{27}O_3NaP$ $[M+Na]^+$: 285.1590; found: 285.1586.

3-Chlorohex-5-enylbenzene (7j)

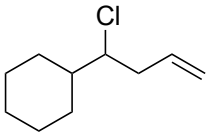


$C_{12}H_{15}Cl$
MW: 194.09

From **1j** (281 mg, 1.0 mmol) following **GP9**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **7j** contaminated with an undetermined product, as a colorless oil (131 mg, 0.67 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 5.91 – 5.76 (m, 1H), 5.14 – 5.09 (m, 2H), 3.89 (dddd, *J* = 10.5, 8.3, 4.6, 2.8 Hz, 1H), 2.89 (ddd, *J* = 14.0, 8.5, 5.7 Hz, 1H), 2.73 (ddd, *J* = 15.3, 9.0, 4.3 Hz, 1H), 2.52 (app t, *J* = 6.5 Hz,

2H), 2.11 – 1.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 134.0, 128.53, 128.48, 126.1, 118.0, 61.6, 42.8, 39.4, 32.6. IR (neat): 3063, 3026, 2947, 1495, 1454, 991, 917, 744, 697, 614 cm^{-1}. HRMS (EI) calcd. for $C_{12}H_{15}Cl$ $[M]^+$: 194.0855; found: 194.0857.

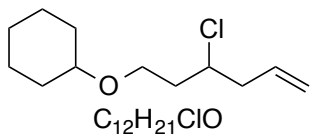
1-Chlorobut-3-enylcyclohexane (7k)



$C_{10}H_{17}Cl$
MW: 172.10

From **1k** (259 mg, 1.0 mmol) following **GP9**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **7k** as a colorless oil (66 mg, 0.38 mmol, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddt, J = 17.3, 10.5, 6.8 Hz, 1H), 5.15 – 5.09 (m, 2H), 3.81 (dt, J = 7.9, 5.0 Hz, 1H), 2.58 – 2.42 (m, 2H), 1.87 – 1.58 (m, 6H), 1.27 – 1.13 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 117.4, 68.4, 43.5, 39.8, 30.2, 28.0, 26.3, 26.2, 26.0. IR (neat): 2924, 2853, 1456, 739, 688 cm^{-1}. HRMS (EI) calcd. for $C_{10}H_{17}Cl$ [M]+: 172.1013; found: 172.1009.

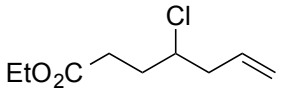
3-Chlorohex-5-enoxycyclohexane (7l)



$C_{12}H_{21}ClO$
MW: 216.13

From **1l** (303 mg, 1.0 mmol) following **GP9**. The product was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **7l** as a colorless oil (139 mg, 0.64 mmol, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 19.2, 9.7, 6.9 Hz, 1H), 5.16 – 5.10 (m, 2H), 4.15 (dtt, *J* = 7.3, 5.3, 3.8 Hz, 1H), 3.61 (dd, *J* = 7.2, 4.9 Hz, 2H), 3.27 – 3.19 (m, 1H), 2.61 – 2.44 (m, 2H), 2.04 (dtd, *J* = 14.4, 7.2, 3.7 Hz, 1H), 1.91 – 1.79 (m, 3H), 1.75 – 1.68 (m, 2H), 1.56 – 1.46 (m, 1H), 1.33 – 1.16 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 118.0, 77.7, 64.3, 59.5, 42.9, 38.4, 32.4, 32.1, 25.9, 24.14, 24.12. IR (neat): 2930, 2855, 1644, 1449, 1363, 1107, 1090, 993, 917, 612 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{21}OClNa$ $[M+Na]^+$: 239.1171; found: 239.1173.

Ethyl 4-chlorohept-6-enoate (7m)



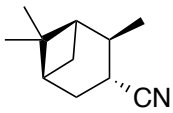
$C_9H_{15}ClO_2$
MW: 190.08

From **1m** (277 mg, 1.0 mmol) following **GP9**. The product was purified by two FCC (1st FCC: silica gel (*n*-pentane/CH_2Cl_2 9:1); 2nd FCC: neutral aluminium oxide (*n*-pentane to *n*-pentane/Et_2O 1:1)) to afford **7m** as a colorless oil (80 mg, 0.42 mmol, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.5, 9.7, 6.9 Hz, 1H), 5.18 – 5.11 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.98 (dtd, *J* = 9.7, 6.4, 3.4 Hz, 1H), 2.63 – 2.43 (m, 4H), 2.16 (dddd, *J* = 15.6, 8.4, 7.1, 3.4 Hz, 1H), 1.92 (dddd, *J* = 14.4, 9.7, 8.0, 5.9 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 133.9, 118.4, 61.6, 60.7, 42.9, 32.9, 31.3, 14.4. IR (neat): 2981, 2926,

1731, 1375, 1249, 1162, 1031, 993, 919, 609 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{16}ClO_2$ $[M+H]^+$: 191.0839; found: 191.0833.

4.7 From General Procedure 10: Radical deboronative cyanations to furnish 8e, 8o, and 8i

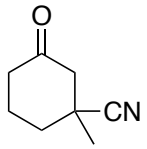
(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptane-3-carbonitrile (8e)



$C_{11}H_{17}N$
MW: 163.14

From **1e** (264 mg, 1.0 mmol) following **GP10**. The product was purified by FCC on silica gel (*n*-pentane/TBME 9:1) to afford **8e** as a colorless oil (96 mg, 0.59 mmol, 59%). Spectral and physical data were in accordance with the literature.[26] $[\alpha]_D^{20}$ – 35.3° (*c* 1.00, $CHCl_3$ (HPLC grade, stabilized on EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (dt, *J* = 10.5, 7.3 Hz, 1H), 2.51 – 2.34 (m, 3H), 2.15 (ddd, *J* = 13.7, 6.8, 2.5 Hz, 1H), 2.00 (tt, *J* = 6.0, 3.1 Hz, 1H), 1.87 (td, *J* = 5.9, 5.2, 1.9 Hz, 1H), 1.22 (s, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 10.1 Hz, 1H), 0.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.0, 47.0, 42.1, 40.5, 38.3, 34.1, 32.1, 28.2, 26.5, 23.1, 21.6.

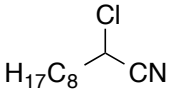
1-Methyl-3-oxocyclohexane-1-carbonitrile (8o)



$C_8H_{11}NO$
MW: 137.08

From **1o** (238 mg, 1.0 mmol) following **GP10**. The product was purified by FCC on silica gel (*n*-pentane/TBME 95:5 to 8:2) to afford **8o** as a colorless oil (56 mg, 0.41 mmol, 41%). Spectral and physical data were in accordance with the literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (dt, *J* = 14.6, 1.8 Hz, 1H), 2.51 – 2.38 (m, 1H), 2.36 – 2.12 (m, 3H), 2.11 – 2.00 (m, 2H), 1.76 (ddd, *J* = 13.9, 7.3, 6.3 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 122.7, 51.1, 40.2, 36.8, 35.6, 26.3, 22.3.

2-Chlorodecanenitrile (8i)

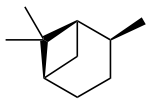


$C_{10}H_{18}ClN$
MW: 187.11

From **1i** (288 mg, 1.0 mmol) following **GP10**. The product was purified by FCC on silica gel (*n*-pentane to *n*-pentane/Et_2O 96:4) to afford **8i** as a colorless oil (148 mg, 0.79 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (t, *J* = 6.9 Hz, 1H), 2.16 – 1.85 (m, 2H), 1.66 – 1.47 (m, 2H), 1.45 – 1.24 (m, 10H), 0.89 (app t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.3, 42.7, 36.5, 31.9, 29.3, 29.2, 28.6, 25.8, 22.8, 14.2. IR (neat): 2925, 2856, 1464, 723, 487 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{18}ClN$ $[M+Na]^+$: 210.1020; found: 210.0914.

4.8 From General Procedures 11 and 12: Reductions to furnish 9d–e, 9i–m, and 12

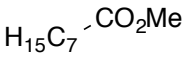
(1*R*,2*S*,5*R*)-2,6,6-Trimethylbicyclo[3.1.1]heptane (9e)



$C_{10}H_{18}$
MW: 138.14

NMR yields: from **1e** (264 mg, 1.0 mmol) following **GP11** to afford **9e** in 58% NMR yield.

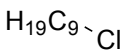
Methyl octanoate (9d)



$C_9H_{18}O_2$
MW: 158.24

From **1d** (283 mg, 1.0 mmol) following **GP11**. The product was purified by FCC on neutral aluminium oxide (heptanes/EtOAc 98:2) to afford **9d** as a colorless oil (79 mg, 0.50 mmol, 50%). The spectral data of **9d** was compared to a commercial sample (CAS: 111-11-5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.30 (app t, J = 7.5 Hz, 2H), 1.69 – 1.53 (m, 2H), 1.36 – 1.19 (m, 8H), 0.87 (app t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 51.6, 34.3, 31.8, 29.3, 29.1, 25.1, 22.7, 14.2.

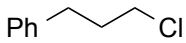
1-Chlorononane (9i)



$C_9H_{19}Cl$
MW: 162.12

From **1i** (289 mg, 1.0 mmol) following **GP11**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **9i** as a colorless oil (129 mg, 0.79 mmol, 79%). Spectral and physical data were in accordance with the literature.[28] **NMR yields:** from **1i** (86.6 mg, 0.3 mmol) following **GP12** to afford **9i** in 91% NMR yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (t, J = 6.8 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.45 – 1.40 (m, 2H), 1.28 – 1.26 (m, 10H), 0.88 (app t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.2, 32.7, 31.9, 29.4, 29.2, 28.9, 26.9, 22.7, 14.1.

3-Chloropropylbenzene (9j)

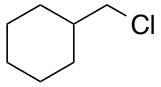


$C_9H_{11}Cl$
MW: 154.06

From **1j** (281 mg, 1.0 mmol) following **GP11**. The product was purified by FCC on silica gel (heptanes 100%) to afford **9j** as a colorless oil (87 mg, 0.56 mmol, 56%). Spectral and physical data were in accordance with the literature.[29] **NMR yields:** from **1j** (84 mg, 0.3 mmol) following **GP12** to afford **9j** in more than 95% NMR yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H),

7.22 – 7.17 (m, 3H), 3.51 (t, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.12 – 2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 128.54, 128.49, 126.1, 44.2, 34.0, 32.8.

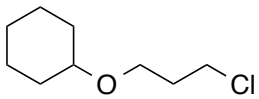
Chloromethylcyclohexane (9k)



$C_7H_{13}Cl$
MW: 132.07

From **1k** (259 mg, 1.0 mmol) following **GP12**. The product was purified by FCC on silica gel (*n*-pentane 100%) to afford **9k** as a colorless oil (92 mg, 0.69 mmol, 69%). Spectral and physical data were in accordance with the literature.[30] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (d, *J* = 6.4 Hz, 2H), 1.86 – 1.57 (m, 5H), 1.34 – 0.93 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1, 40.3, 30.8, 26.2, 25.8.

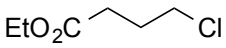
3-Chloropropoxycyclohexane (9l)



$C_9H_{17}ClO$
MW: 176.10

From **1l** (303 mg, 1.0 mmol) following **GP11**. The product was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **9l** as a colorless oil (100 mg, 0.57 mmol, 57%). **NMR yields:** from **1l** (303 mg, 1.0 mmol) following **GP11** to afford **9l** in 75% NMR yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.4 Hz, 2H), 3.58 (t, *J* = 5.9 Hz, 2H), 3.27 – 3.19 (m, 1H), 2.00 (p, *J* = 6.2 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.74 – 1.72 (m, 2H), 1.55 – 1.49 (m, 1H), 1.33 – 1.16 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.6, 64.0, 42.2, 33.2, 32.2, 25.8, 24.1. IR (neat): 2923, 2853, 1456, 1110 cm^{-1}. HRMS (EI) calcd. for $C_9H_{17}ClO$ $[M]^+$: 176.0960; found: 176.0962.

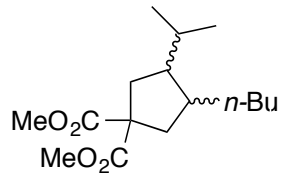
Ethyl 4-chlorobutanoate (9m)



$C_6H_{11}ClO_2$
MW: 150.05

From **1m** (277 mg, 1.5 mmol) following **GP11**, EtOH was used instead of MeOH. The product was purified by FCC on neutral aluminium oxide (*n*-pentane 100%) to afford **9m** as a colorless oil (46 mg, 0.30 mmol, 30%). Spectral and physical data were in accordance with the literature.[31] **NMR yields:** from **1m** (111 mg, 0.4 mmol) following **GP12** (EtOH was used instead of MeOH) to afford **9m** in 75% NMR yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.12 – 2.07 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 60.6, 44.1, 31.3, 27.7, 14.2.

Dimethyl 3-butyl-4-isopropylcyclopentane-1,1-dicarboxylate (12)



$C_{16}H_{28}O_4$
MW: 284.20

From **11** (205 mg, 0.5 mmol) following **GP11**. The product was purified by FCC on silica gel (heptanes/EtOAc 98:2) to afford **12** as a 8:2 mixture of diastereomers, as a colorless oil (65 mg, 0.23 mmol, 46%). *Mixture of diastereomers:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 8H), 2.59 (d, *J* = 7.5 Hz, 0.2H), 2.48 (dd, *J* = 13.0, 7.3 Hz, 0.2H), 2.43 – 2.27 (m, 2.2H), 2.20 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.93 – 1.76 (m, 1.7H), 1.75 – 1.44 (m, 4H), 1.41 – 1.20 (m, 5.8H), 1.16 – 1.07 (m, 2H), 0.95 – 0.83 (m, 11H), 0.79 (d, *J* = 6.8 Hz, 1H). *Major diastereomer:* ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.8, 58.8, 52.8, 52.7, 51.8, 40.5, 38.3, 37.4, 30.1, 28.4, 26.6, 22.9, 22.1, 21.9, 14.2. IR (neat): 2953, 2931, 1732, 1434, 1248, 1195, 1144, 732 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{29}O_4$ $[M+H]^+$: 285.2060; found: 285.2055.

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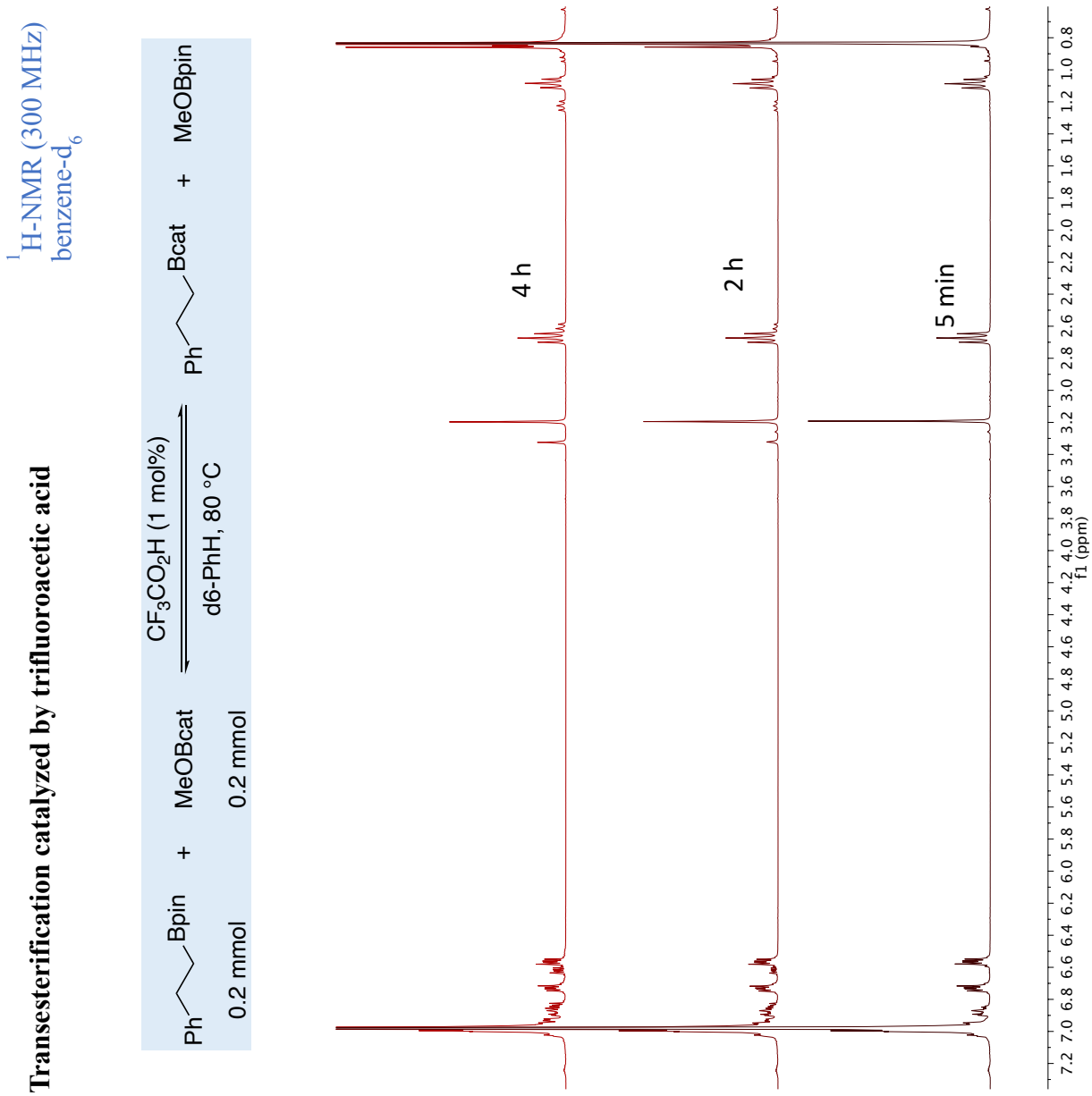
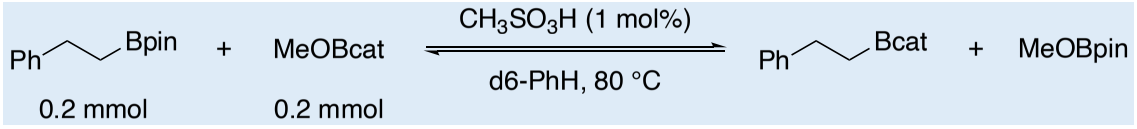
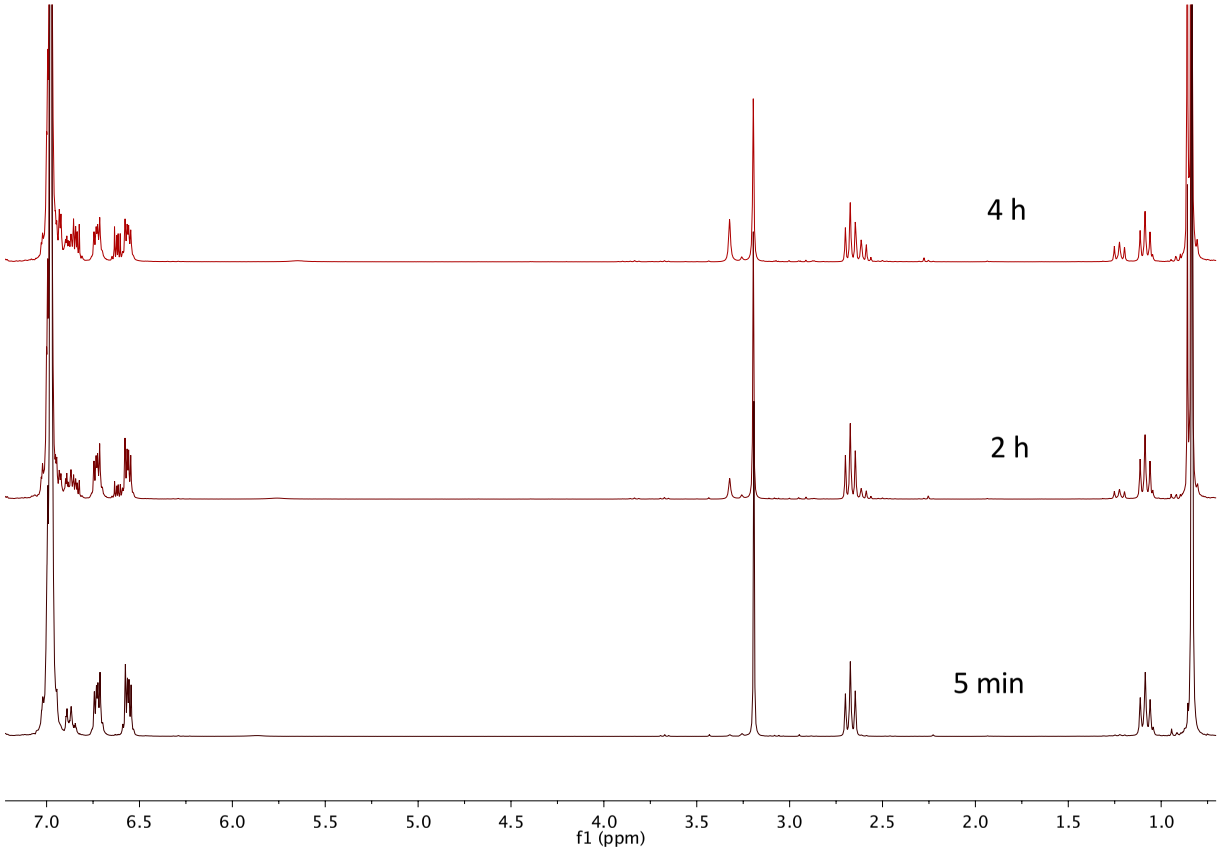
6 Monitoring of transesterification by ^{1}H NMR



Transesterification catalyzed by methanesulfonic acid

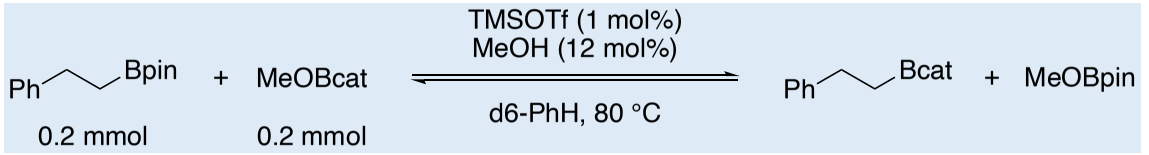
^{1}H-NMR (300 MHz)
benzene-d_6

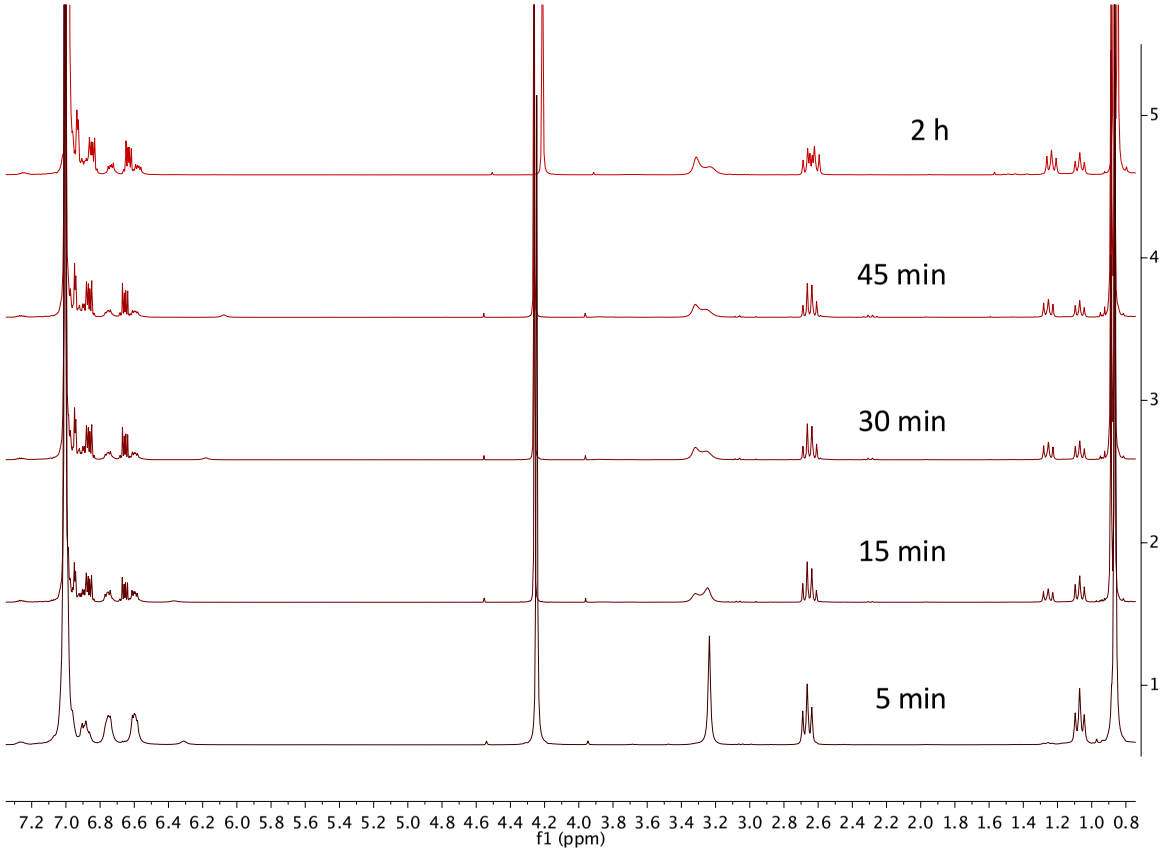




Transesterification catalyzed by trifluoromethanesulfonic acid

^{1}H-NMR (300 MHz)
benzene-d_6





3

Hydromethylation of Unactivated Alkenes

Unpublished Results

The work discussed in this chapter was conducted in collaboration with Dr. Tappin who conceived it, laid out foundational work, and brought invaluable guidance along the way (in supplement to Prof. Renaud!). Experimentation discussed from Section 3.2.2 onwards is my contribution.

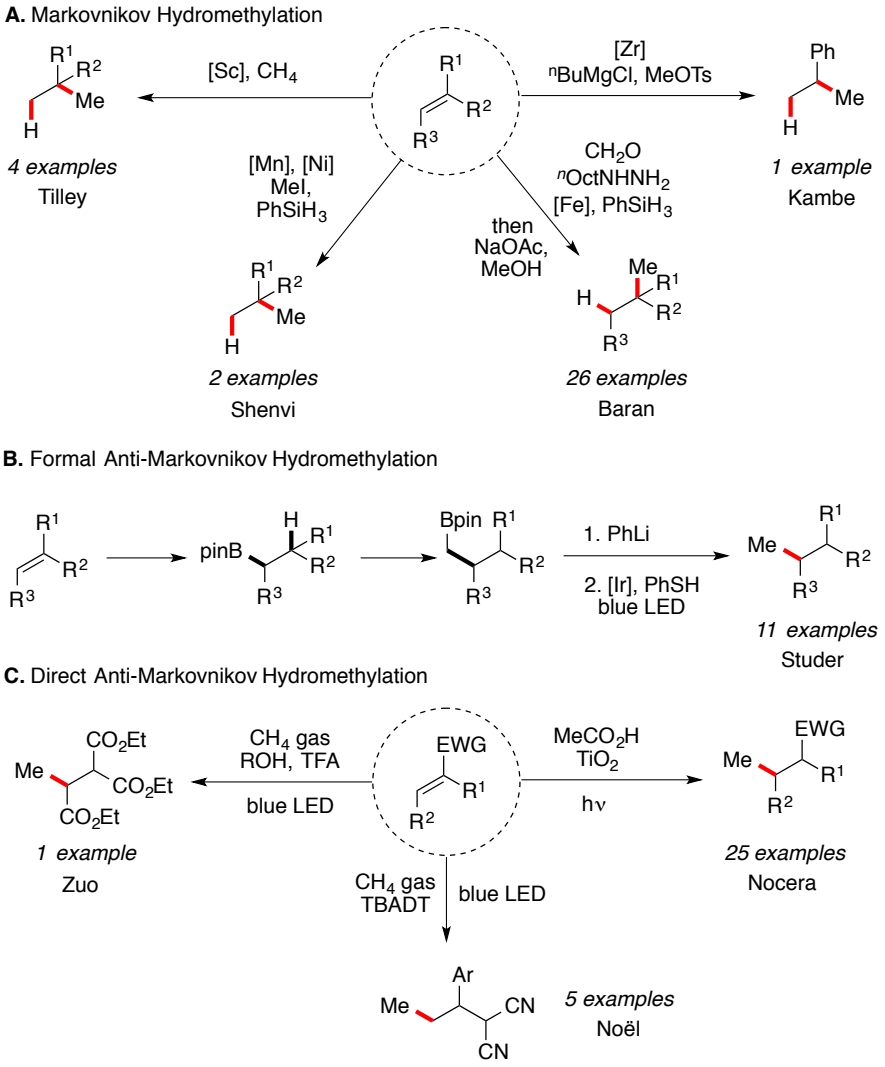
3. Hydromethylation of Unactivated Alkenes

3.1. Introduction

The transformation of unsaturated hydrocarbons into saturated analogues *with the introduction of a functional group* is of great interest for synthetic chemists. Although many methods have been developed over the years, little precedent exists for the direct hydromethylation of unactivated alkenes, highlighting the difficulties to accomplish such a transformation. Furthermore, most of the sparse existing methods are a direct Markovnikov hydromethylation of alkenes, whereby the methyl group becomes attached at the most substituted carbon atom of the C—C π-bond (Scheme 1, **A**). For instance, protocols involving activation of methane by scandium complexes were reported.[1,2] However, only four examples of hydromethylation were provided with this strategy due to the pyrophoric properties and the selectivity of the catalyst. Another system using methyl tosylate (MeOTs) catalyzed by a zirconocene complex was reported by Kambe and co-workers where the Markovnikov hydromethylation was restricted to styrenes.[3] In 2015 Baran and co-workers developed a creative protocol applicable to unactivated alkenes, which proceeds through an alkyl hydrazide formation followed by a reductive C—N bond cleavage.[4] However, this one-pot process has defined limitations such as product isolation (e.g. due to homodimerization and reduction of by-products) and tricky experimental set up. Finally, Shenvi and co-workers reported two examples of hydromethylation of alkenes using the combination of mangenese-mediated metal hydride hydrogen atom transfer (MHAT) catalysis and nickel-catalysis to form quaternary carbon centers.[5]

In 2019 Studer and co-workers developed a formal anti-Markovnikov hydromethylation employing a hydroboration/Matteson homologation/protodeboronation strategy, where the regioselectivity is controlled in the initial hydroboration step (Scheme 1, **B**).[6] To the best of our knowledge, this protocol is the first anti-Markovnikov-type hydromethylation of *unactivated* alkenes. Recently, strategies relying on photoredox catalysis have emerged to access methyl radicals with subsequent addition across *activated* alkenes. For instance, the use of flow technology was investigated using either cerium photocatalysis or decatungstate photocatalysis for the C—H functionalization of gaseous alkanes. In this case, hydromethylation proceeded exclusively on activated and tri-substituted alkenes (Scheme 1, **C**).[7,8] Another protocol, based on decarboxylation of acetic acid, mediated by titanium oxide, was also reported for the

hydromethylation of alkenes, although the scope of this transformation was restricted to Michael acceptors (Scheme 1, **C**).[9] The large absence in the literature for an anti-Markovnikov hydromethylation of alkenes, along with lack of functional group tolerance of the existing methods, prompted us to investigate a general method to achieve this transformation on unactivated alkenes.



Scheme 1. Strategies for the hydromethylation of alkenes

We considered a reaction sequence merging our previous work on iodine atom transfer radical addition (I-ATRA) reactions of iodomethylboronic acid pinacol ester (ICH_2Bpin) over unactivated alkenes[10] with the radical protodeboronation of pinacol boronic esters (Scheme 1,

D).[11] In our design, the well-established reaction manifold of the Kharasch reaction during the I-ATRA functionalizes the alkene with an electrophilic iodide. Next, we envisioned to doubly reduce the resulting γ-iodoalkylboronic ester by means of radical-deiodination of the secondary iodide and radical-protodeboronation of the boronic ester. Due to the high reactivity of transient radical intermediates, the overall process would be mild, functional-group tolerant, and highly selective. We can see this by considering the individual synthetic transformations. The I-ATRA step of this process is chemoselective towards terminal alkenes in the presence of electron-rich and electron-deficient internal alkenes. Regioselectivity of this C1-radical donor reagent onto the terminal position of the alkene is effectively exclusive, to predestine the hydromethylation anti-Markovnikov. The second and third steps of the process generate secondary- and primary-alkyl radicals, whose reduction with numerous H-atom donor reagents operate with fast and efficient chains. Because both these alkyl radicals are nucleophilic, they can be reduced by the *same type* of H-atom donor reagent. Any unreacted iodide or alkene from the first step does not catastrophically interfere with C—I or C—B reductions in the subsequent steps. Consequently, by thoughtful design and solvent selection, the overall process can be telescoped into one pot and becomes simple to operate.

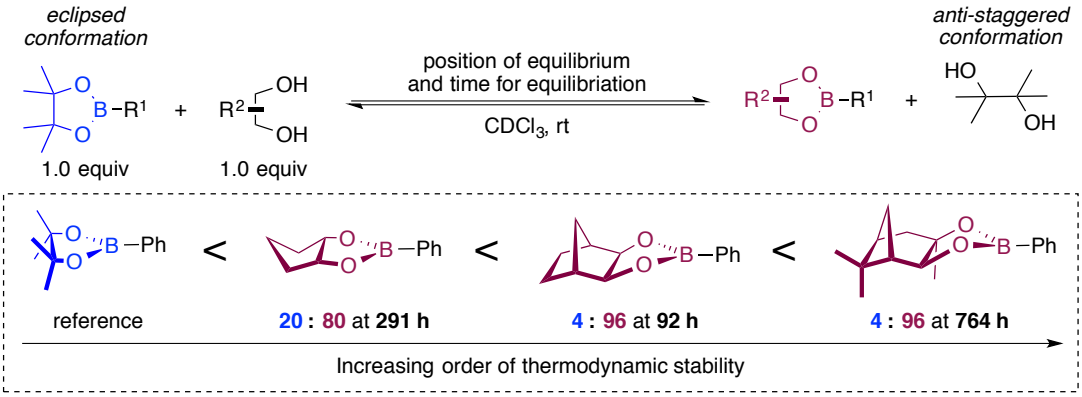
3.2. Initial Investigations

3.2.1 ATRA Initiated by DLP

Previous investigations on the ATRA process showed that the isolation of pinacol γ-iodoalkylboronic esters resulting from the reaction of ICH_2Bpin over terminal alkenes was challenging due to their instability on silica gel.[12] We decided to examine the stability of boronic esters made from other diols since their thermodynamic stability was known to differ (Scheme 2).[13] Here, the position of equilibrium indicates the thermodynamics of the boron-transesterification from a pinacol boronic ester to another boronic ester. Going from the left-hand side to the right-hand side of the equilibrium, an acyclic diol is liberated in exchange for a cyclic diol. In the original publication, the converse of these experiments has been performed to approach equilibrium from the other side of the equation in order to confirm ratios and times (i.e., using a complementary mixture of diols and boronates).

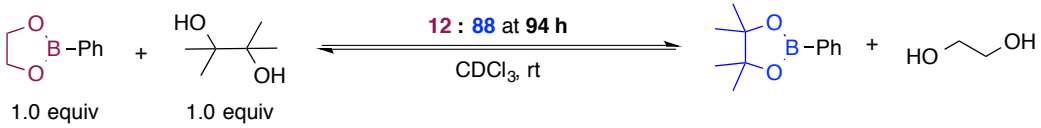
There are three possible driving forces pulling the position of equilibrium to the right-hand side. Entropic reasons can account for the major effect. An acyclic diol has more possible

conformations when it is no longer bound as the cyclic boronate and so the increase in its degrees of freedom as it is liberated will pull the position of equilibrium to the right-hand side when it is being exchanged with a cyclic diol. The same principle is in operation when comparing the position of equilibrium between a monocyclic diol and a bicyclic diol because a bicycle has fewer (or no) conformations.



Scheme 2. Relative thermodynamic stability of some boronic esters

Another entropic effect to consider is the release of torsional strain from groups bonded to the alcoholic carbon atom when this type of diol is liberated. Specifically, considering the eclipsing methyl groups in the pinacol boronic ester. One could imagine that a great release of eclipsing strain would encourage the position of equilibrium to move towards the free pinacol side. However, pinacol will displace glycol from its boronic ester (Scheme 3).[14] Therefore, we must make the following deduction: either i) free pinacol has more allylic strain than the pinacol boronic ester, or ii) other enthalpic or stereoelectronic factors overcome strain. It is likely that the second reason is the real reason, and this makes sense because it is often the case that bonding beats sterics.



Scheme 3. Transesterification of 2-(phenyl)-1,3,2-dioxaborolane with pinacol

One clue to support this idea is that 6-membered ring boronates are much less stable than their 5-membered counterparts. The closer to planarity the ring is, the better the oxygen lone pairs can delocalize into the boron p_z orbital. This could explain the unique ubiquity that pinacolato boronic esters have in chemistry: they are thermodynamically more stable than those

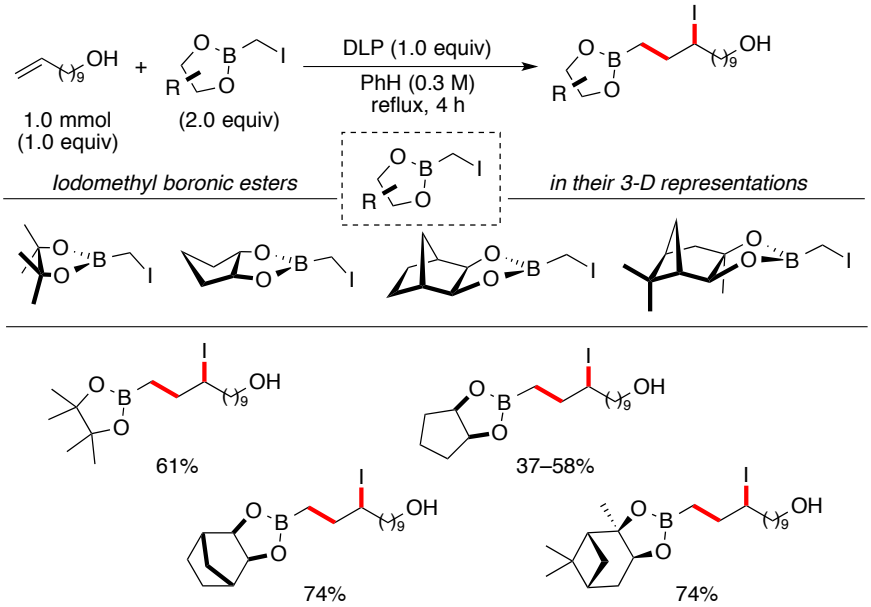
of monocyclic ethylene glycol, 1,2-propanediol and *meso*-2,3-butanediol. Curiously, the same phenomena can explain the kinetic stability of pinacolato boronic esters. The four methyl groups effectively shield or block access to the reactive site (the boron atom). Additionally, the Lewis acidity of the boron is also reduced due to the greater ability of the oxygen lone pairs to feed into the vacant boron p_z orbital.

With all these effects in mind, we set ourselves the objective of finding a diol that gave a more stable boronic ester than the pinacolato one. It turns out, empirically, that *all* 5-membered ring *cis*-1,2-diols will have a position of equilibrium on the right-hand side when being exchanged with pinacol. Now, the interesting point is to *compare where* that position of equilibrium is for different diols when they are all coming from (referenced to) a pinacol boronic ester (Scheme 2). So, we can tease out the conclusion that the boronic ester with *cis*-cyclopentane-1,2-diol (20:80) is thermodynamically less stable than the one with *exo,exo*-2,3-norbornanediol or pinanediol (both 4:96).

Here comes the subtle point: Since we wish to incorporate a transesterification of the chosen boronic ester with catechol at some point downstream in our designed reaction sequence, we actually need a diol that gives us a boronic ester thermodynamically more stable then Bpin yet is also kinetically unstable. *exo,exo*-2,3-Norbornanediol fits the bill perfectly. It's boronic ester is just as stable as the most stable possible, *yet it will undergo transesterification an order of magnitude faster!* We believe that norbornane diol has the potential to replace pinacol as the diol of choice for all the classical organoboron chemistry, giving boronic esters that are more stable yet seemingly paradoxically more labile, and with only slightly more complicated NMRs.

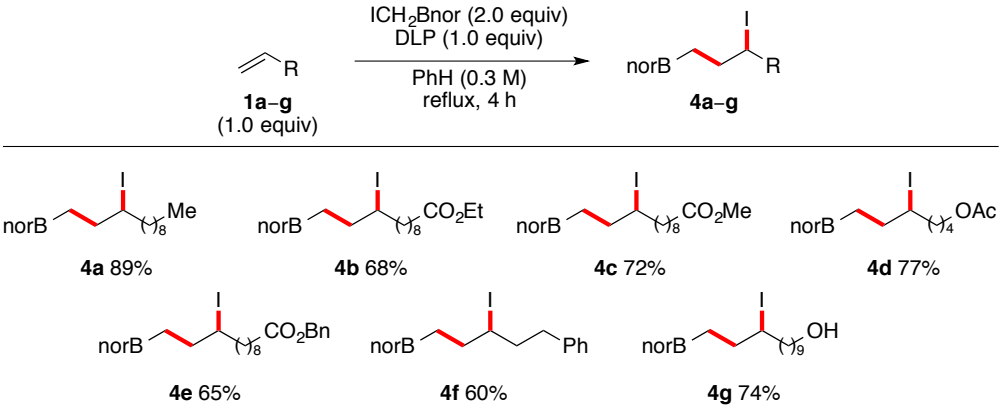
During his PhD in the Renaud group, Dr. Tappin performed a systematic study of the ATRA reaction using different types of iodomethyleneboronic ester radical precursors (Scheme 4).[12] We are making the assumption that reactivity doesn't differ much between these four iodides, however this is absorbed by the fact that we are interested to compare reaction outcomes *after* flash column chromatography isolation. We wanted to be able to isolate clean γ-iodoboronic esters. We assume that increased thermodynamic stability correlates to a reduction in product loss during silica gel chromatography (which turns out to be correct). The ATRA product (and radical precursor) derived from *cis*-cyclopentane-1,2-diol proved to be very unstable to silica gel so provided the ATRA product in widely varying yields after chromatography. As expected, norbornanediol and pinanediol boronic ester radical precursors gave the best results. There were apparent (by TLC analysis) improved conversions and yields

for ATRA over some alkenes with the norbornanediol-derived radical precursor, however it is worth noting that no significant general difference was seen between the two. More significant however, was the difference in complexity in interpretation of the NMR spectra of products; thus, in addition to the transesterification requirements discussed previously, we decided to investigate further the ATRA process employing the iodomethylboronic acid ester with the symmetrical norbornanediol (ICH_2Bnor).



Scheme 4. ATRA using different iodomethyl boronic esters (reported yields are after isolation by FCC on silica gel)

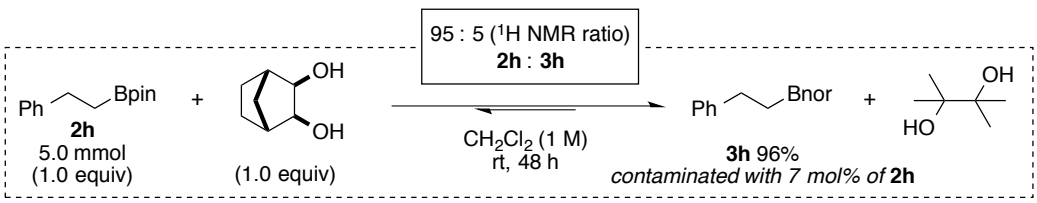
The results summarized in Scheme 5 show the overall yields for the formation of ATRA products using iodomethylboronic esters as radical precursor and dilauroyl peroxide (DLP) as initiator. Reaction times of 4 h were beneficial for the full decomposition of DLP when refluxing in EtOAc. Reaction times of 1.5 h were sufficient when refluxing in benzene, however there was no detriment to the yield when those times were extended to 4 h. The high loadings of DLP (0.8–1.4 equiv) turned out to be necessary, with 1.0 equiv being optimal, to achieve best conversions and yields as determined from the aforementioned cyclopropanation investigations. These conditions were not extensively re-optimized for this study. Isolation of the norbornanediol-derived ATRA products **4a–g** could now be achieved (whereas previously with the pinacol analogues significant decomposition occurred on silica gel) and are summarized in Scheme 5.



Scheme 5. DLP-initiated ATRA of ICH_2Bnor over some terminal alkenes (yield of isolated product)

3.2.2 Radical protodeboronation

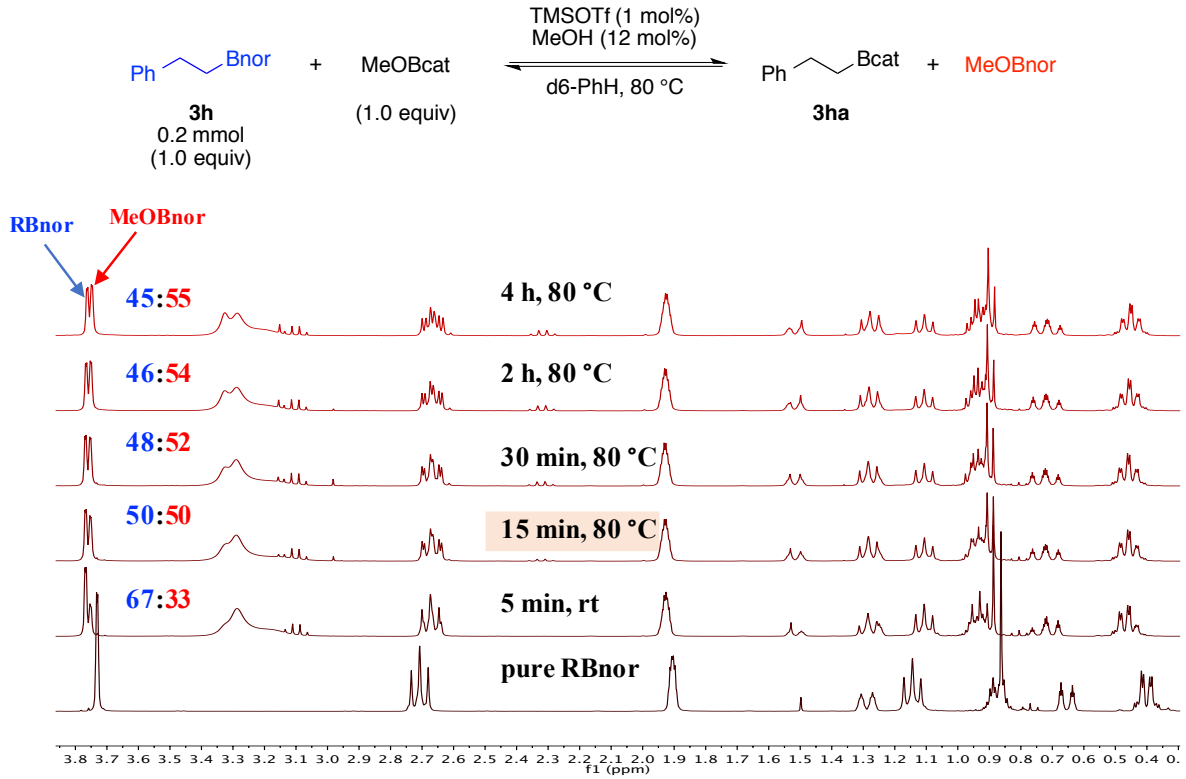
Having established efficient reaction conditions for the ATRA process using ICH_2Bnor, we turned our attention to the protodeboronation step. We decided to explore the use of our previously developed reaction conditions for the protodeboronation of alkyl pinacol boronic esters.[11] Therefore, we sought to study the transesterification of alkyl norbornanediol boronic ester (RBnor) to alkyl catechol boronic ester (RBcat) using MeOBcat. The use of 2-phenylethyl norbornanediol boronic ester **3h** was selected for ease of comparison of spectral data (i.e., expected difference of chemical shift between the α-boryl peaks of RBnor and RBcat). Thus, the synthesis of the precursor 2-phenylethyl norbornanediol boronic ester was achieved by transesterification of the corresponding alkyl pinacol boronic ester **2h** with norbornanediol. As expected by thermodynamic stability factors, a 95:5 equilibrium (determined by ^1H NMR) in favor of **3h** was observed at room temperature (Scheme 6).



*Scheme 6. Preparation of **3h** via transesterification of **2h** with norbornanediol (yield of isolated product)*

With boronic ester **3h** in hand, we subjected it to the boron-transesterification process with MeOBcat. Pleasingly, the appearance of new benzylic protons at 2.79 ppm (t, J = 8.2 Hz, 2H)

was detected but an overlap with the benzylic protons of **3h** (2.80 ppm [t, J = 8.1 Hz, 2H]) did not allow estimation of the equilibrium (Scheme 7). Unfortunately, the α-boryl protons (1.41 ppm [t, J = 8.2 Hz, 2H]) of the RBcat generated also overlapped with a signal from the norbornane moiety (1.42 ppm [ddt, J = 10.9, 3.8, 2.2 Hz, 1H]) of precursor **3h**. Therefore, the transesterification equilibrium was determined using the downfield protons from the norbornane moiety of **3h** (α to oxygens, 3.90 ppm [d, J = 1.2 Hz, 2H]), and the doublet formed at 3.88 ppm (d, J = 1.2 Hz, 2H), tentatively assigned as being norbornanediol methyl borate (MeOBnor). Integrations of the two peaks showed that transesterification was already occurring after five minutes at room temperature, in a 67:33 ^{1}H NMR ratio (**3h**:**3ha**), and that an equilibrium was reached after 15 minutes at 80 °C.

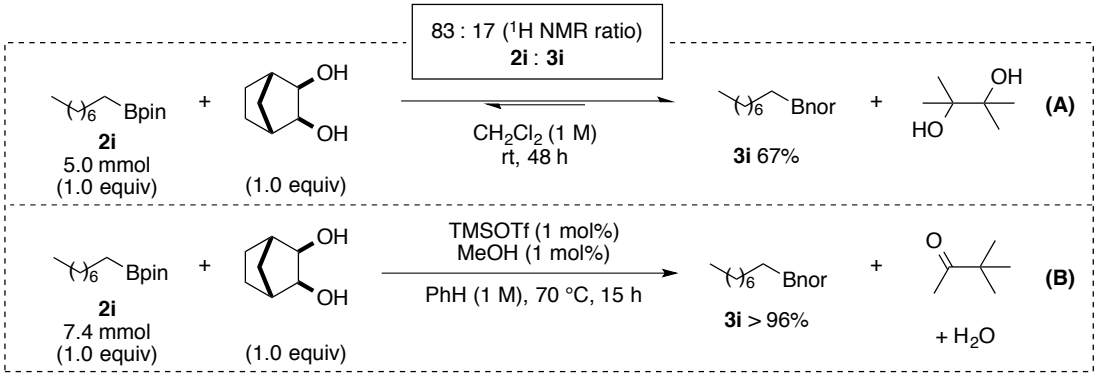


*Scheme 7. Transesterification of **3h** with MeOBcat followed by ^{1}H NMR*

When using the pinacol boronic ester **2h** (see Chapter 2), no transesterification took place at room temperature. These observations go in the direction of Roy and Brown's work who showed the kinetic instability of norbornanediol boronic esters (equilibration was achieved in 92 h) towards transesterification relative to the more kinetically stable pinanediol and *cis*-cyclopentanediol boronic esters (equilibrations were achieved in 291 and 764 h). As shown in Scheme 6 and in agreement with Roy and Brown's studies (see Scheme 2), the greater

thermodynamic stability of norbornanediol boronic esters compared to pinacol boronic esters, yet their kinetic instability, highlight the interesting reaction properties of norbornanediol boronic esters.

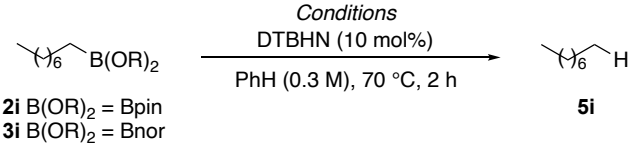
Having established that boron-transesterification of **3h** mediated by MeOBcat was possible, we started to investigate the radical protodeboronative chain process using *n*-octylnorbornanediol boronic ester **3i**. It was prepared by transesterification of the corresponding alkylpinacol boronic ester **2i** with norbornanediol (Scheme 8). Surprisingly, a modest 83:17 equilibrium (determined by ^{1}H NMR) was observed, causing challenges during product isolation (very close R_f between the two boronic esters by TLC) (Scheme 8, **A**). In retrospect, employing 1.1 or even 1.05 equiv of norbornanediol should have been enough to effectively make this a clean conversion. Nonetheless, we had another trick up our sleeve: An acid catalyzed transesterification was performed in order to use Le Chatelier's principle and the pinacol rearrangement to drive the equilibrium towards full conversion of **2i** to **3i** (Scheme 8, **B**).[15]



*Scheme 8. (A) Transesterification of **2i** with norbornanediol. (B) Acid catalyzed transesterification of **2i** with norbornanediol. Yield of isolated product*

Having the *n*-octylnorbornanediol boronic ester **3i** in hand, we started to investigate the protodeboronation reaction in more detail. The results of optimizations are summarized in Table 1. GC yields were performed due to the volatility of the octane **5i** formed. In agreement with our previous results on the protodeboronation of alkylpinacol boronic esters, acid catalyzed transesterification using *tert*-butyl catechol (TBC) gave promising yields after two hours, reaching even 87% after 16 h at 70 °C (Table 1, entry 1). This latest result suggests that traces of air could re-initiate our radical chain process. Surprisingly, when no acid catalyst was used,

similar yield was obtained after two hours (Table 1, entry 2). A similar result was obtained when substoichiometric amount of catechol were generated *in-situ* from MeOBcat and methanol (Table 1, entry 3).[16] Curiously, the yield greatly improved by using TBC and 5.0 equivs of methanol simultaneously (Table 1, entry 4). The use of the more acidic pentafluoro-1-propanol did not improve but rather decreased the yield, as did a Lewis-base (Table 1, entries 5–6). Next, the best reaction conditions were tested under air initiation which afforded the protodeboronated product **5i** although in lower yield (Table 1, entry 7). Eventually, the corresponding *n*-octylpinacol boronic ester **2i** was treated under our optimized reaction conditions (i.e. TBC, methanol and di-*tert*-butylhyponitrite (DTBHN)) and only 21% of **5i** was formed (Table 1, entry 8). This result is in good agreement with our transesterification studies indicating a faster formation of the catechol boronic ester intermediate when starting from the norbornanediol boronic ester moiety. In other words, this observation supports the higher kinetic stability of pinacol boronic ester relatively to norbornanediol boronic esters, making the latter as a the most suitable boronic ester in term of thermodynamic stability and reactivity for transesterification processes.



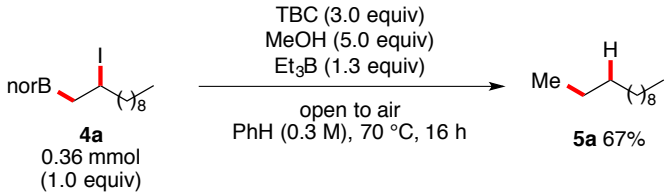
Entry	*n*-$C_8H_{17}B(OR)_2$ (0.4 mmol, 1.0 equiv)	Catechol source (equiv)	Additive (equiv)	GC yield after 1 h	GC yield after 2 h
1	3i	TBC (2)	TfOH (0.01)	37%	57%[b]
2	3i	TBC (2)	-	33%	55%
3	3i	MeOBcat (0.3)	MeOH (5)	46%	58%
4	3i	TBC (2)	MeOH (5)	61%	82%
5	3i	TBC (2)	$F_3CCF_2CH_2OH$ (5)	46%	66%
6	3i	TBC (2)	HMPA	47%	51%
7[a]	3i	TBC (2)	MeOH (5)	50%	57%
8	2i	TBC (2)	MeOH (5)	19%	21%

[a]open to air; [b]87% o/n; nonane as internal standard

Table 1. Optimization of the radical protodeboronative chain process

Next, we turned our attention to the development of a sequence leading to the reduction of the γ-iodoalkylnorbornanediol boronic ester. One avenue of investigation we explored was to perform a one-pot deiodination/protodeboronation sequence. Keeping in mind that catechol sources such as TBC are excellent hydrogen atom donors for alkyl radicals and have been used in radical-mediated deiodination reactions,[17] we decided to combine the protodeboronation and the deiodination processes by addition of triethylborane (Et_3B). Hence, this strategy was tested on the isolated ATRA product **4a** resulting from the reaction of ICH_2Bnor over 1-undecene

(Scheme 9). Pleasingly, under air initiation and in presence of 1.3 equivs of Et_3B, the reaction afforded **5a** in 67% GC yield over the two steps in a one-pot protocol.

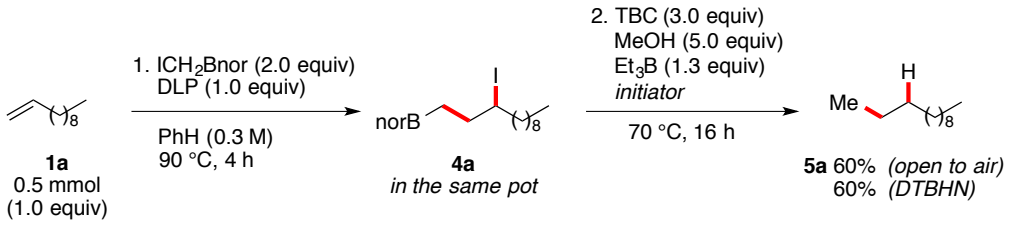


Scheme 9. Development of a one-pot deiodination/protodeboronation sequence (GC yield)

3.3. Hydromethylation: One-Pot Approach

3.3.1 Preliminary results

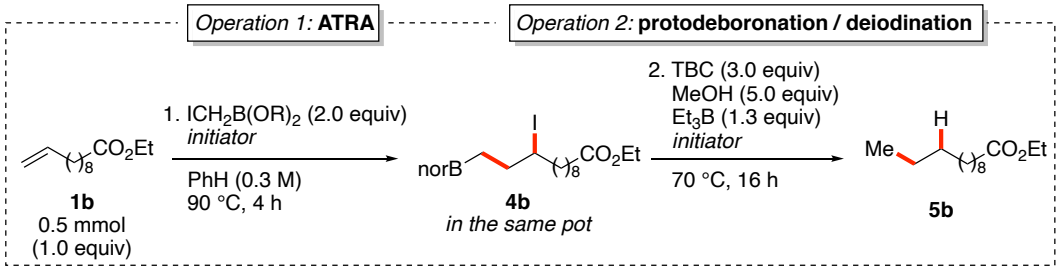
Very pleased by this result, we examined a one-pot procedure involving an ATRA from the reaction of ICH_2Bnor over a terminal alkene followed by concurrent protodeboronation and deiodination of the γ-iodoalkylnorbornanediol boronic ester intermediate. By performing the different processes in the same solvent, we could circumvent any solvent switch or work-up of the ATRA intermediate. In order to do so, we had to perform the ATRA step in benzene (it turns out to be the solvent of choice for the protodeboronation rather than the more benign EtOAc which isn't compatible with the protodeboronation). Therefore, we envisaged to successively add TBC, methanol and Et_3B to crude **4a** after full decomposition of the DLP initiator. Pleasingly, the one-pot hydromethylation of **1a** gave good yield over these three synthetic transformations by two operations. No improvement was seen by changing to DTBHN (inert atmosphere) for the initiation of the second operation (Scheme 10).



Scheme 10. Development of a one-pot ATRA/deiodination/protodeboronation sequence (GC yields)

3.3.2 Optimizations of the one-pot process

Next, we wanted to explore the scope and confirm the generality of these results by testing different functionalized terminal alkenes. Thus, ethyl 10-undecenoate **1b** was selected and engaged in the one-pot hydromethylation protocol (Table 2). Under DTBHN initiation, the corresponding hydromethylated product **5b** was obtained in moderate yield after two hours (Table 2, entry 1). When using air initiation, a slight difference in yield was observed whether the system was flushed with air and subsequently closed or fully open to air for the entire reaction time (Table 2, entries 2–3). These results suggest that high concentration of air contributes to competitive oxidation of the alkyl radical intermediates. In good agreement with previous results, the use of substoichiometric amount of DLP (i.e. 0.5 equiv) lowered the yield by half (Table 2, entry 4).[12] Besides, subjecting the old-generation radical precursor, ICH_2Bpin, to the hydromethylation protocol resulted in drastic decreases of the yield (Table 2, entry 5). Eventually, we tried a Et_3B/air initiated ATRA process which mostly resulted in the recovery of the alkene (Table 2, entry 6). All these observations are in confirmation of Dr. Tappin's results.



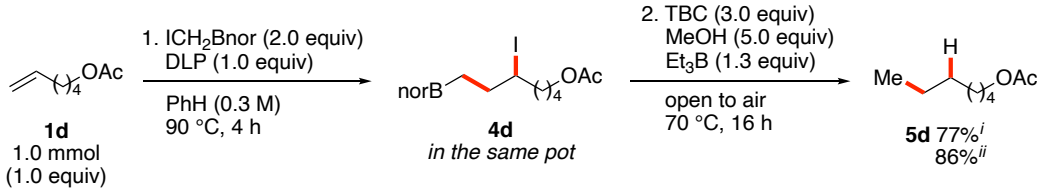
Entry	$ICH_2B(OR)_2$ $B(OR)_2$ =	initiator (operation 1)	initiator (operation 2)	GC yield after 2 h	GC yield after 3.5 h	GC yield after 16 h
1	RBnor	DLP (1 equiv)	DTBHN	46%	54%	-
2	RBnor	DLP (1 equiv)	air (stopper)	28%	40%	74%
3	RBnor	DLP (1 equiv)	open to air	-	-	63%
4	RBnor	DLP (0.5 equiv)	air (stopper)	-	-	39%
5	RBpin	DLP (1 equiv)	air (stopper)	-	-	23%
6	RBnor	Et_3B (2x1 equiv)[Ψ]	open to air	-	-	23%

[Ψ]room temperature, 16 h

Table 2. Optimizations of the hydromethylation sequence

In order to cross check the GC yield obtained, isolation of the hydromethylated product was performed. Therefore, ethyl 10-undecenoate **1b** was subjected to the best reaction conditions and isolated by column chromatography. However, it turned out that the resulting **5b** had a similar polarity with some of DLP decomposition by-products, resulting in a challenging purification process. For this reason, we performed the reaction on another

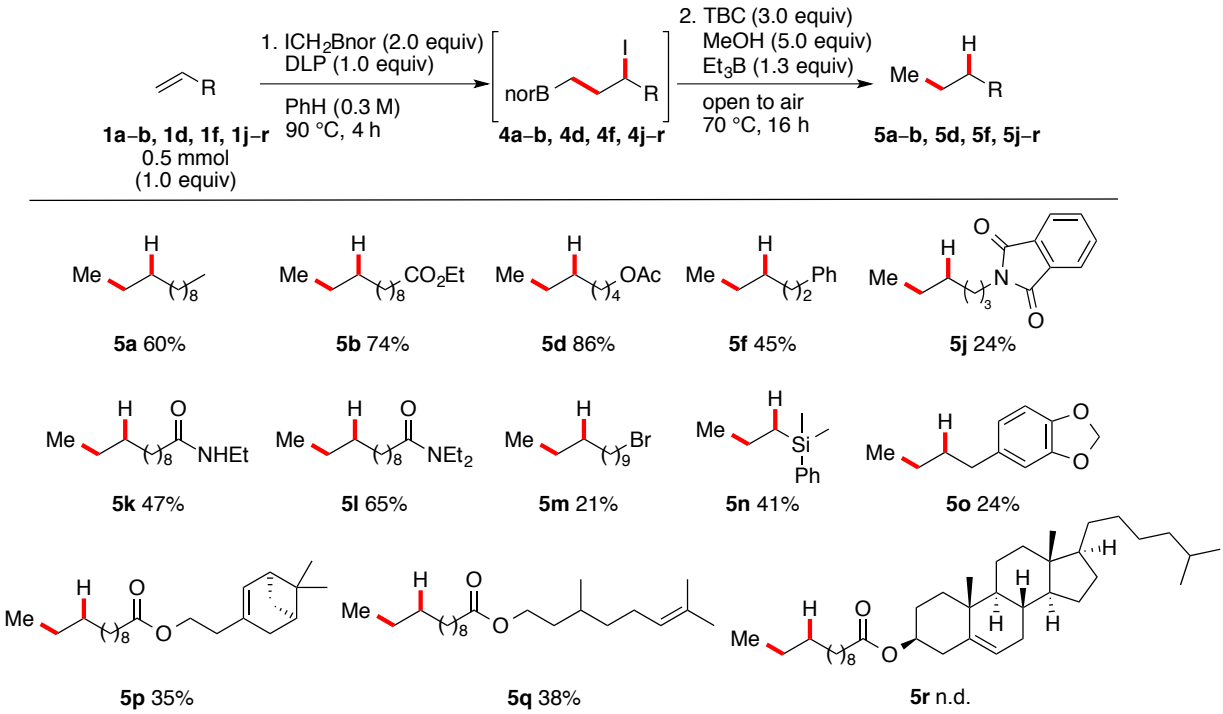
substrate for which the corresponding hydromethylated compound generated would have a polarity that allows easier isolation. Thus, 5-hexenyl acetate **1d** was used and pure **5d** could be easily obtained with an isolated yield matching well the GC yield measured previously (Scheme 11).



*Scheme 11. Isolation of the hydromethylated compound **5d** to confirm GC yield. [i] Yield of isolated product. [ii] GC yield*

3.3.3 Scope of the hydromethylation sequence

With the optimized reaction conditions in hand, we began to investigate the substrate scope of the sequence using a series of unactivated terminal alkenes (Scheme 12). GC yields were performed to prevent false results caused by challenging isolations from DLP decomposition by-products. Simple terminal alkenes bearing an ester, an acetate, a phenyl, a secondary or a tertiary amide and a silane moiety gave the desired products **5b**–**f**, **5k**–**l** and **5n** in fair to good yields (41–86%). Unsurprisingly, safrole **1o** proved to be particularly low yielding since possible hydrogen atom transfer (HAT) side reactions were expected from the weak benzylic-allylic C—H bonds. However, we were pleased to obtain non-zero yields for such a challenging substrate in a radical chemistry setting; this is likely an unanticipated consequence of such a high initiator loading. As can be expected by the short alkyl chain (three methylenes) separating the alkene reaction site from a phthalimide moiety, **5j** was obtained in poor yields, possibly due to the decomposition of the ATRA product intermediate by intramolecular substitution of the iodide atom by the oxygen lone pair of the amide. However, we did not anticipate that bromide **5m** would be low yielding. A plausible explanation could be the simple substitution of the bromide atom by the excess of methanol, which, if further confirmed, can be easily prevented by decreasing the stoichiometric ratio of the alcohol used.



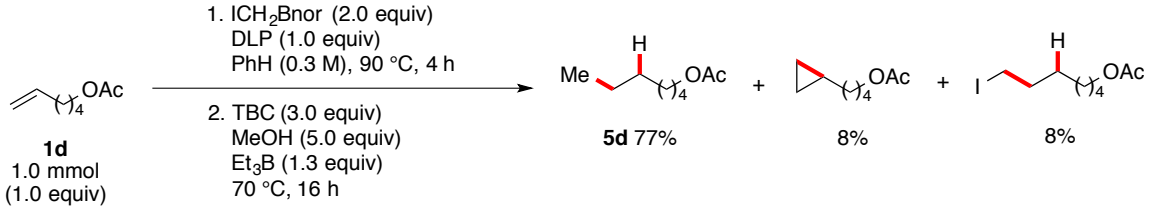
Scheme 12. Scope of the hydromethylation sequence (GC yields)

Next, we examined a series of dienes in order to test the chemoselectivity of the reaction (Scheme 12). However, the nopol and citronellol derivatives **1p**–**q** gave the hydromethylated compounds **5p**–**q** in poor yields. Considering the significant weight of the cholesterol derivative **5r**, GC yields could not be provided for its preparation. In this specific example, ^{1}H NMR yield could not be performed since the chemical shift of the newly introduced methyl group overlapped with aliphatic protons. Furthermore, the integration of other protons would give false results due to the presence of any unconverted γ-iodoboronic ester intermediate (**4r**). In light of the results obtained for **5p–q**, we hypothesized that the excess of methanol could result in the carboxylic transesterification with the ester group, even though this presumption has not been examined yet. Therefore, the nopol derivative **1p** was engaged in the deiodination/protodeboronation step in the absence of methanol but did not result in improved yields (Scheme 13). Next, the photostability of intermediate **4p** was questioned. Therefore, the hydromethylation sequence was next performed both protected from light and exposed to a sun lamp (300 W, ca. 3 cm from the reaction flask) and resulted in similar yields, allowing us to exclude this hypothesis (Scheme 13). At this point in time, we did not examine further the reactivity of the dienes and focused our attention on side-reactions resulting from the deiodination/protodeboronation process.

*Scheme 13. Preliminary optimizations of the chemoselective hydromethylation reaction using **1p** (GC yields)*

3.3.4 Side reactions observed

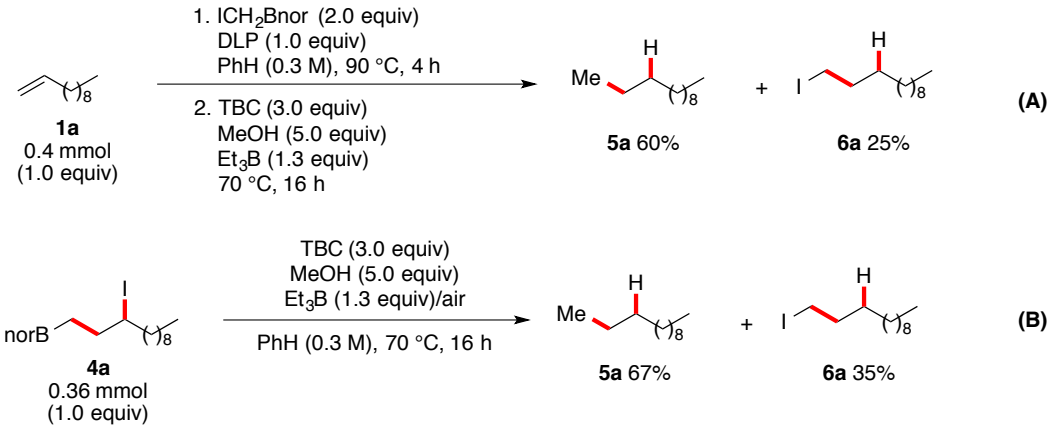
When performing the hydromethylation using **1d**, a mixture of primary iodide and cyclopropane was isolated (Scheme 14). In fact, thanks to the characteristic ^{1}H NMR chemical shifts of a terminal, alkyl cyclopropane ring (typically 0.8 – 0.5 ppm (m, 2H), 0.5 – 0.2 ppm (m, 1H), 0.1 – –0.1 ppm (m, 2H)), its formation was easily identified in most of the crude residues of the hydromethylation sequence. However, we were surprised by the formation of a primary alkyl iodide, generated by iodine atom transfer either from the ATRA product intermediate or from the radical precursor ICH_2Bnor. The primary alkyl iodide from productive DLP initiation, was identified separately so that we could say this primary alkyl iodide was arising from a different pathway.



*Scheme 14. Discovery of side-reactions during hydromethylation of **1d** (yield of isolated product)*

This side reaction was further confirmed by performing the hydromethylation of **1a**. Indeed, GC analysis of the crude product residue revealed a significant amount of iododododecane **6a** formed (Scheme 15, **A**). In parallel, the pure γ-iodonorbornanediol boronic ester **4a** was subjected to the deiodination/protodeboronation protocol and a greater amount of iodine atom abstraction was observed (Scheme 15, **B**). This result shows that this process occurs readily from the γ-iodonorbornanediol boronic ester intermediate **4a** but does not dismiss a possible iodine atom transfer from the excess of radical precursor ICH_2Bnor. It is worth mentioning that

high concentration of the ATRA products (0.3 M) was used in the deiodination/ protodeboronation sequence, promoting intermolecular iodine atom transfer processes. Therefore, further investigations are ongoing to prevent this side reaction by mean of dilution factors. The formation of alkyl cyclopropane ring has not been quantified in these experiments although its formation was identified by ^{1}H NMR spectroscopy.

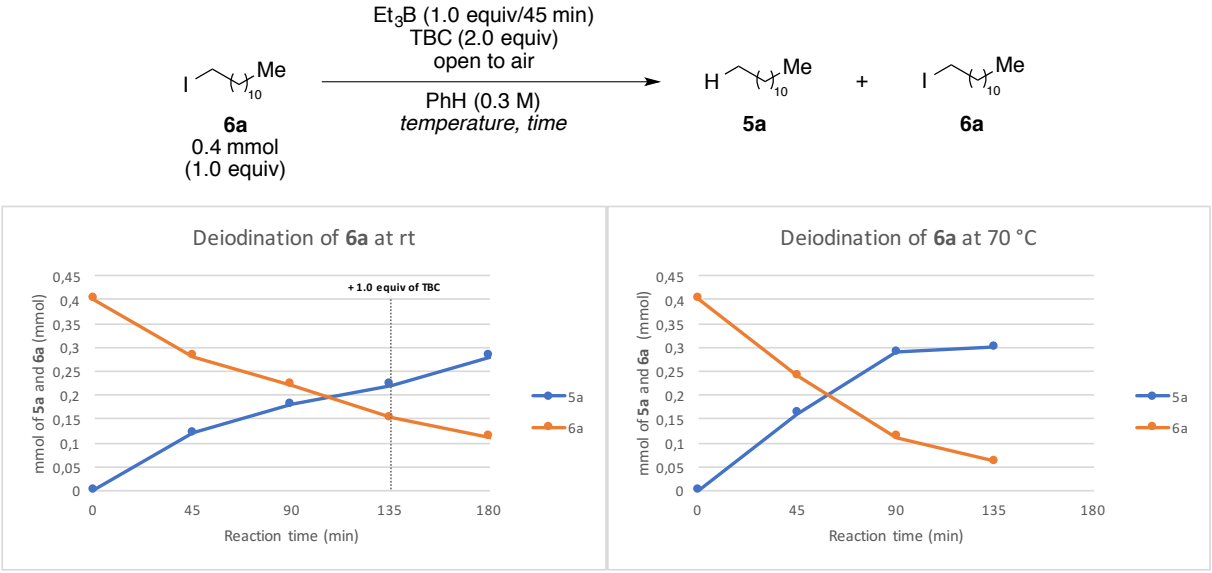


*Scheme 15. Confirmation of iodine atom transfer while performing either hydromethylation of **1a** or either deiodination/protodeboronation of **4a** (GC yields)*

3.4. Hydromethylation: Sequential Approach

3.4.1 Preliminary results

Considering the predominance of this iodine atom transfer process, we had to find conditions to reduce it during the hydromethylation sequence. We tackled this problem firstly, by focusing on these types of compounds independently. To do so, we examined first the deiodination of iodododecane using the system Et_3B/TBC (Scheme 16). When performed at room temperature, 30% of deiodinated product **5a** was observed after 45 min, while slightly higher conversion was observed by heating up the reaction to 70 °C. Adding two to three more equivalents of Et_3B every 45 minutes proved to be beneficial to the reaction with up to 75% of yield obtained at 70 °C after 135 minutes. However, this method becomes unattractive due to the amount of Et_3B required to reach acceptable yields. Indeed, at low concentration of the primary alkyl iodide, competitive reduction of the ethyl radicals becomes predominant, requiring continuous addition of radical initiator and preventing the deiodination process to reach completion.



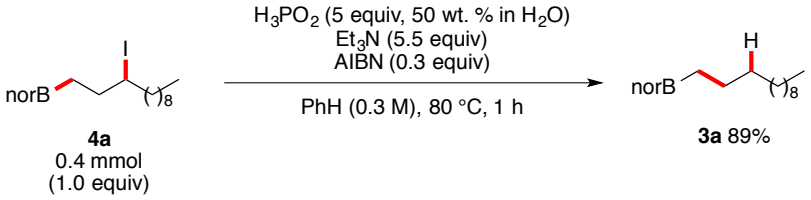
*Scheme 16. Deiodination of primary alkyl iodide **6a** using Et_3B/air and TBC (GC yields). Another equivalent of TBC was added after 135 min (deiodination at rt)*

Next, we investigated a thiol-catalyzed deiodination process previously developed in our group.[18] As anticipated, the deiodinated product **5a** was obtained in low yield presumably due to the slower iodine atom transfer between the ethyl radical and **6a** in comparison with secondary and tertiary alkyl iodides.[17] We were also unsuccessful when using Barton's reaction deiodination conditions (hypophosphorous salt).[19]

3.4.2 Toward a sequential ATRA/deiodination process

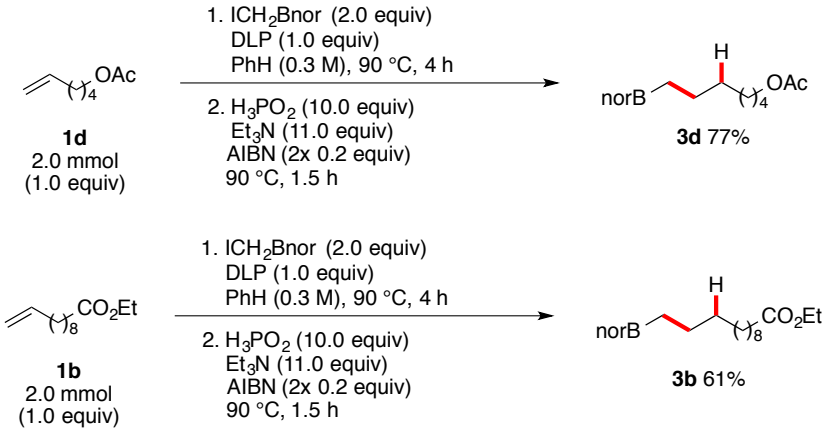
Another approach to tackle this issue was to perform the deiodination of the γ-iodonorbornanediol boronic ester derivative before protodeboronation. Therefore, we isolated **4a** resulting from the ATRA reaction of ICH_2Bnor over 1-undecene. When treated with hypophosphorous acid and triethylamine in boiling dioxane, the corresponding deiodinated compound **3a** was isolated in moderate 50% yields even though full consumption of **4a** was observed. With the aim of performing the deiodination on the crude γ-iodonorbornanediol boronic ester intermediate **4a**, we attempted to perform the hypophosphorous salt mediated deiodination in benzene (Scheme 17). Surprisingly, this solvent resulted in improved yield by using the same molarity as used for the ATRA process. One explanation might be the better miscibility of benzene with the hypophosphorous acid solution used (50 wt. % in water).

Therefore, a route to a one pot sequence involving ATRA followed by deiodination seemed achievable.

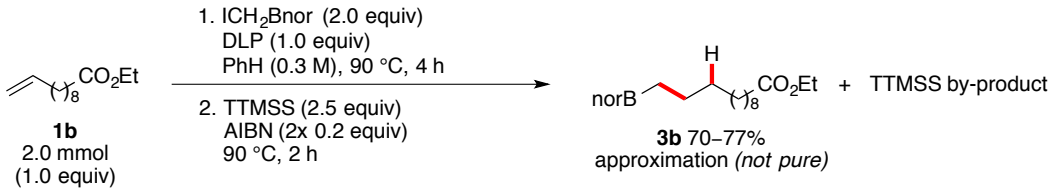


*Scheme 17. Deiodination of secondary alkyl iodide **4a** using Barton's method (yield of isolated product)*

Thus, we started looking at the feasibility of a one-pot sequence involving an ATRA using DLP initiation followed by a hypophosphorous salt mediated deiodination of the resulting γ-iodonorbornanediol boronic ester. Ethyl undec-10-enoate **1b** and 5-hexenyl actetate **1d** were both engaged in the proposed one-pot protocol (Scheme 18). In both cases, addition of a second portion of AIBN proved to be critical to increase conversion and yield. As expected, moderate to good yields over the two steps were obtained. We observed that the miscibility of the organic and aqueous phase containing the hypophorous salt was increased by addition of dioxane or acetonitrile. In contrast, while being higher yielding than the hypophosphorous salt mediated deiodination, the use of tris(trimethylsilyl)silane (TTMSS) gave rise to inseparable mixture of **3b** and silylated by-products (possibly $TTMS_2O$) (Scheme 19).



Scheme 18. Development of a one-pot ATRA/deiodination sequence using Barton's method (yield of isolated product)

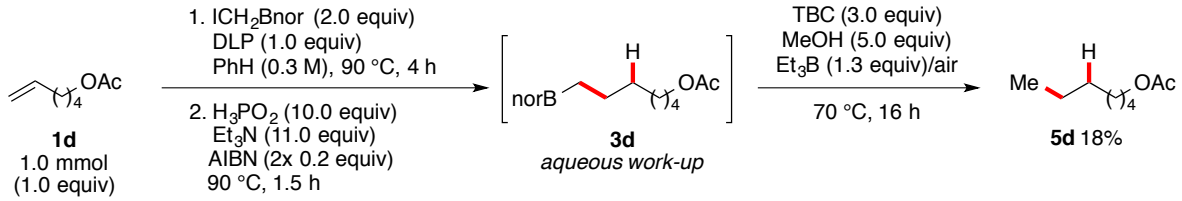


Scheme 19. Development of a one-pot ATRA/deiodination sequence using TTMSS. (yield of isolated product)

3.4.3 Protodeboronation

3.4.3.a. Preliminary investigations

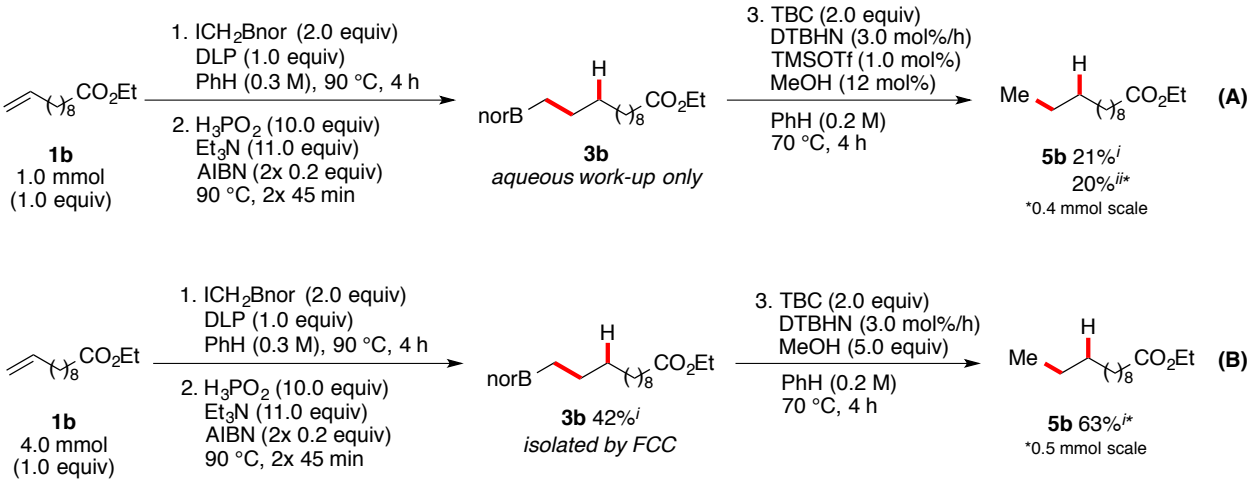
Thus, having suitable reaction conditions for the ATRA/deiodination sequence, we started to investigate a one-pot process involving radical protodeboronation. Our straightforward idea was to perform an aqueous workup after deiodination in order to remove the highly water-soluble hypophosphorous acid and salt[20] as well as the water which we expected to be critical for performing the protodeboronation. However, when the crude norbornanediol boronic ester residue **3d** was treated under the optimized protodeboronation reaction conditions, an unexpected low yield was obtained (Scheme 20).



*Scheme 20. Protodeboronation of the crude residue **3d** after aqueous work-up (yield of isolated product)*

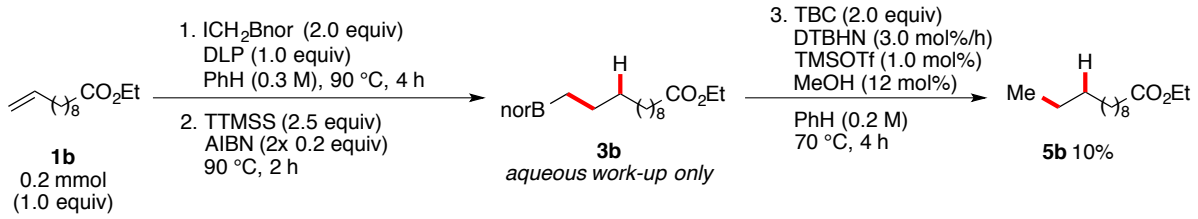
We questioned if an acid catalyst provided by partial decomposition of the γ-iodonorbornanediol boronic ester could be catalyzing the transesterification, or if Et_3B could be involved in the reaction mechanism. To test the first hypothesis, we subjected the crude norbornanediol boronic ester residue **3b** to the acid catalyzed transesterification previously developed for the protodeboronation of pinacol alkylboronic esters (Scheme 21, **A**).[11] The use of DTBHN in combination with triethylborane was examined considering that it generally gives increased yields and better reproducibility compared to air initiation. However, these conditions proved consistently low yielding and ca. 80% of unreacted **3b** was recovered, suggesting that transesterification could be inhibited. Furthermore, these results indicate that acid catalysis is

not involved in the one-pot deiodination/protodeboronation sequence. Additionally, when the crude norbornanediol boronic ester residue **3b** was purified by column chromatography prior to being engaged in the non-acidic catalyzed protodeboronation reaction, compound **5b** was indeed obtained in fairly good yields (Scheme 21, **B**).



*Scheme 21. (A) Acid catalyzed protodeboronation of the crude residue **3b** after aqueous work-up. (B) Protodeboronation of pure **3b** after column chromatography. [i] NMR yield. [ii] GC yields*

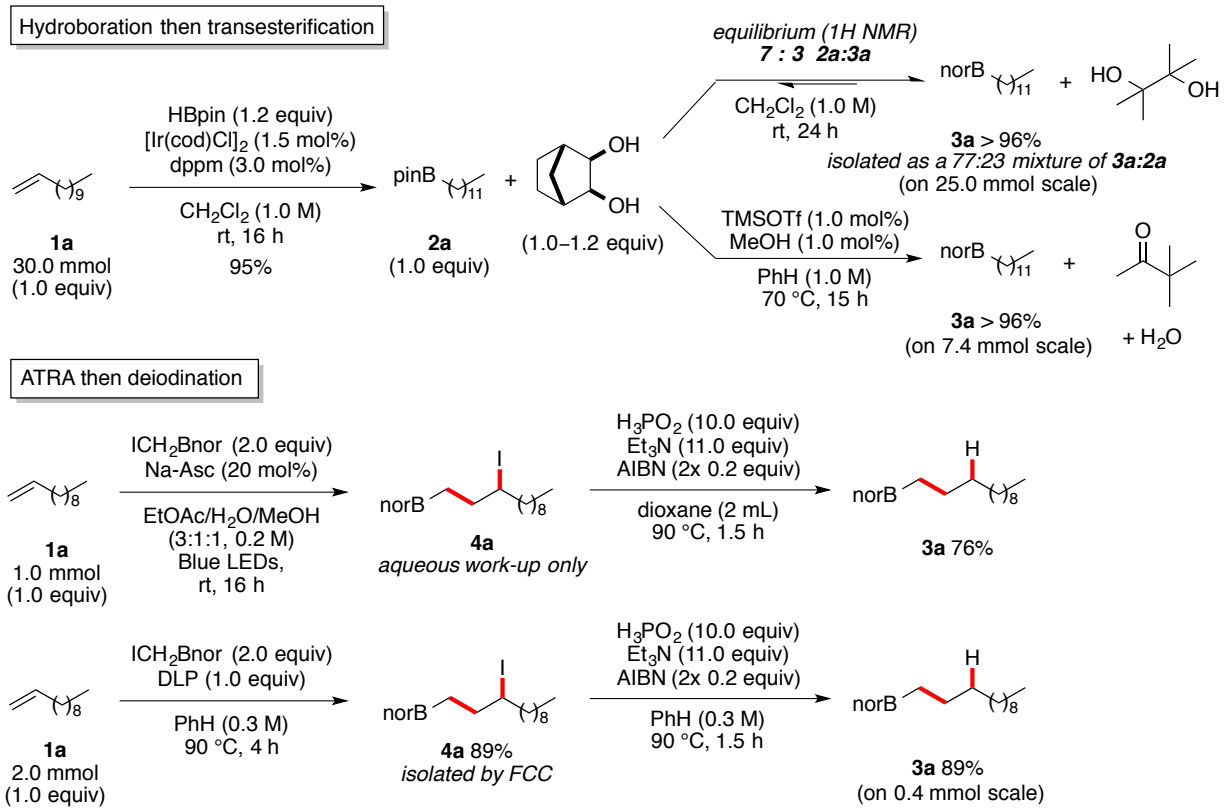
These results being in contradiction with our previous investigations (Scheme 7 and Table 1), we hypothesized that residual hypophosphorous acid and/or salt could inhibit the transesterification. To prevent this outcome, we performed the deiodination using TTMSS and treated the corresponding crude norbornanediol boronic ester residue **3b** under the acid catalyzed protodeboronation reaction conditions. Unfortunately, the same outcome was observed (Scheme 22). Further investigations are ongoing to test the hypothesis that the 1,3-dinitrile form AIBN radical recombination is not inhibiting the deiodination with only 2.0 equivs of TBC. For the moment, preliminary results suggest that employing 5.0 equivs of TBC, along with higher dilutions, improve significantly reaction outcome.



*Scheme 22. ATRA and subsequent deiodination with TTMS of **1b** followed by acid catalyzed protodeboronation of the resulting intermediate **3b** (GC yields)*

3.4.3.b. Study of the influence of potential impurities

At that moment in time, this avenue of investigation turning out to be of dead end, we began our exploration towards the potential role of Et_3B in the protodeboronation process. Beforehand, the simple alkyl boronic ester **3a** was prepared using different methods in order to identify the possible influence of residual by-product on the reproducibility of the protodeboronation reaction. **3a** was prepared by iridium catalyzed hydroboration of dodecene with pinacolborane followed by transesterification of the resulting alkylpinacol boronic ester **2a** with norbornanediol (Scheme 23). The latter was first accomplished at room temperature in dichloromethane and using an excess of the diol, but an equilibrium was reached and did not allow complete separation of the two boronic esters by column chromatography. Thus, an acid catalyzed transesterification was employed in order to perform a pinacol rearrangement which displaces the equilibrium towards the formation of the norbornanediol boronic ester. This second method allowed us to prepare pure **3a** in high yields. Also, we synthetized **3a** by an ATRA reaction initiated with DLP, and a subsequent deiodination with hypophosphorous acid on the isolated ATRA compound **4a**. Some material was as well provided by Nicholas Tappin, who prepared the norbornanediol boronic ester derivative **3a** by an ATRA process of ICH_2Bnor over 1-undecene initiated with blue LEDs (unpublished results), and a subsequent deiodination with hypophosphorous acid on the crude ATRA residue. Next, each derivative **3a** synthesized was treated independently under the protodeboronation reaction conditions and resulted in moderate but reproducible yields (53–60%).

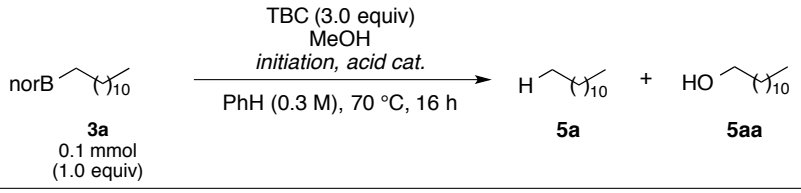


*Scheme 23. Preparation of **3a** by different methods (yield of isolated products)*

3.4.3.c. Studies on the role of triethylborane

Thus, we started to explore the potential influence of Et_3B. Again, when **3a** was subjected to the acid catalyzed protodeboronation reaction, the yield dropped drastically (Table 3, entry 2). The use of a stronger acid such as hydrogen bromide (HBr) was as well investigated in order to reproduce the potential partial decomposition of the ATRA intermediate in a more accurate manner. Surprisingly, while only traces of protodeboronated compound **5a** were detected, it appeared that half of **3a** oxidized to form **5aa** during the process (Table 3, entry 3). This over-oxidation phenomenon might be caused by uncontrolled amount of air in the reaction flask leading as well to fluctuations in yields. Interestingly, addition of stoichiometric amounts of Et_3B together with HBr catalysis resulted in highly increased yield of protodeboronated compound **5a** and simultaneous decreased of oxidized specie **5aa** (Table 3, entry 4). This outcome can be possibly explained by the consumption of air by Et_3B and vice versa, preventing competitive oxidation of the alkyl boronic ester **3a**. Initiation by DTBHN may shut down this competitive process. Pleasingly, **5a** was obtained in fairly good yields when using DTBHN initiation along with HBr catalysis, supporting the existence of competitive oxidation of the boronic ester **3a** by air (Table 3, entry 5). Although we are not confident about the mechanism behind this oxidation reaction, we believe that a radical mechanism is involved, presumably

proceeding via a formation of an alkylperoxy-boronic ester species and subsequent homolytic O—O bond cleavage to generate a stable boroxyl radical and a reactive alkoxyl radical. Next, stoichiometric amounts of Et_3B were added to the HBr-catalyzed protodeboronation initiated by DTBHN in order to consume the residual traces of air (Table 3, entry 6). These reaction conditions resulted in excellent yields for the protodeboronation process, with no traces of oxidized compound **5aa**. Delighted by this result, we investigated the use of substoichiometric amount of Et_3B and found that high yields for the formation of **5a** were consistently obtained whether stoichiometric or catalytic amounts of Et_3B were used (Table 3, entries 7–8). Some more investigations have to be done to fully understand the mechanism of the protodeboronation process, and to ultimately develop a hydromethylation sequence involving subsequent ATRA, deiodination, and protodeboronation. These investigations are now undertaken by Gaetano Geraci.



Entry	Et_3B	initiation	TMSX	MeOH	yield 5a	yield 5aa
1	-	air	-	5.0 equiv	53%	nd
2	-	air	X = OTf	0.12 equiv	31%	nd
3	-	air	X = Br	0.12 equiv	6%	53%
4	1.3 equiv	air	X = Br	0.12 equiv	51%	36%
5	-	DTBHN (10 mol%)	X = Br	0.12 equiv	62%	21%
6	1.3 equiv	DTBHN (10 mol%)	X = Br	0.12 equiv	96%	0%
7	0.5 equiv	DTBHN (10 mol%)	X = Br	0.12 equiv	96%	0%
8	0.2 equiv	DTBHN (10 mol%)	X = Br	0.12 equiv	93%	0%

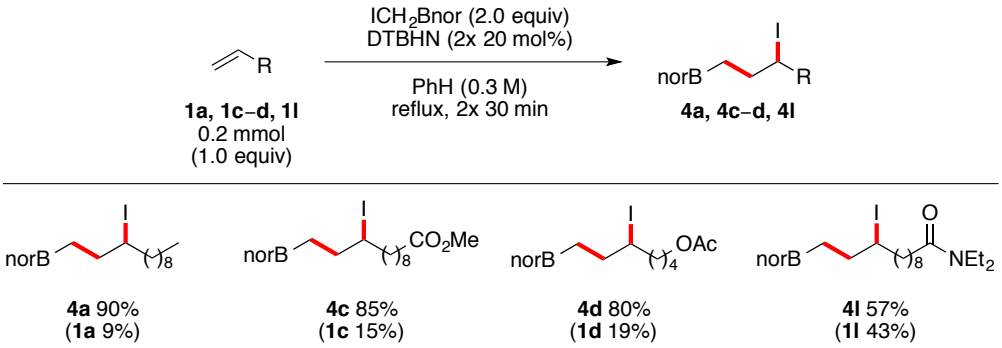
Table 3. Influence of Et_3B on the protodeboronation process (GC yields)

3.5. Going Further: ATRA Initiated by DTBHN

3.5.1 ATRA – Preliminary results

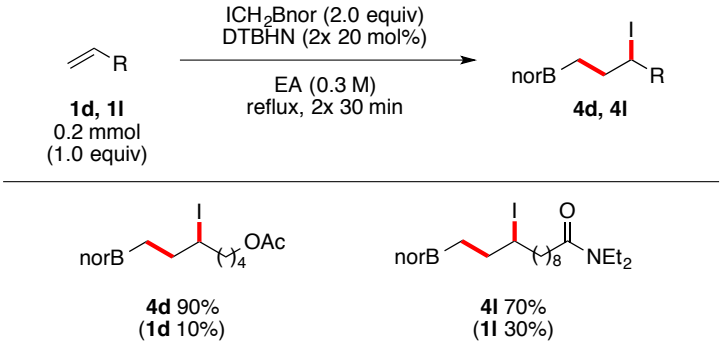
Another avenue of investigation left to explore is the use of a different radical initiator for the ATRA process. Although providing good yields with a wide range of substrates, the use of one equivalent of DLP was required due to many radical chain disruptions. The quantity of

side-products generated by thermal decomposition of DLP was problematic for simple isolation procedures. Recently our group has reported very mild reaction conditions using substoichiometric amounts of DTBHN as an initiator for ATRA (and related) processes, including iodine atom transfer.[21] This protocol generates highly reactive methyl radicals that undergo fast iodine atom transfer to out-compete chain breaking events. Furthermore, the formation of volatile by-products (i.e., acetone and methyl iodide) from productive initiation facilitates product isolation. In such a way, the development of a hydromethylation sequence involving an ATRA process initiated by DTBHN would render this transformation more applicable to preparative applications. On this basis, preliminary investigations were carried out and will be further pursued in our laboratory. Dr. Tappin demonstrated that the radical precursor ICH_2Bpin reacted over 1-undecene with DTBHN initiation to generate the corresponding ATRA product, albeit in low yields. These preliminary results encouraged us to test this initiating system with ICH_2Bnor and to investigate the scope of the method. We set up the reaction using the simple 1-undecene as radical trap in refluxing benzene to anticipate an eventual one-pot protocol involving subsequent deiodination and protodeboronation processes (Scheme 24). The transformation proceeded smoothly and afforded **4a** in excellent yield. Other alkenes were tested and the ATRA products **4c** and **4d** were obtained in fairly good yields along with remaining unreacted alkene. However, functional group compatibility appeared to be limited as illustrated by the moderate yield obtained for ATRA product **4l**. The recovery of the unreacted alkene **1l** suggests an inefficient iodine atom transfer process. It is likely that the greater challenges encountered by DTBHN as opposed to DLP could be related to side-reactions of *tert*-butoxyl radicals (with, for example, H-atoms weakened by proximity to functional groups).



Scheme 24. ATRA initiated by DTBHN in refluxing benzene for the reaction of ICH_2Bnor over terminal alkenes (NMR yields)

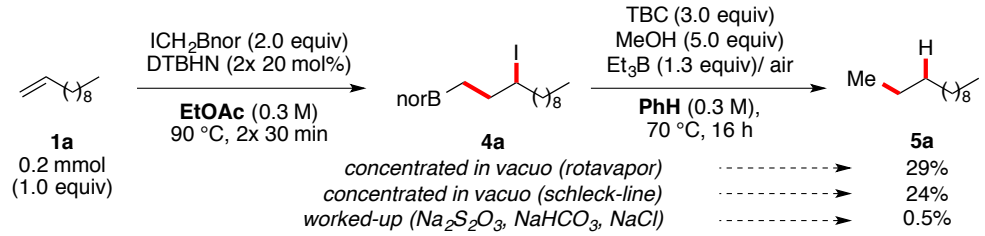
Therefore, the synthesis of **4d** and **4l** were conducted in ethyl acetate in order to favor the β-scission of *tert*-butoxyl radicals to methyl radicals (Scheme 25).[21] As expected, a noticeable increase in yield was detected for the formation of both ATRA products **4d** and **4l**.



Scheme 25. ATRA initiated by DTBHN in refluxing ethyl acetate for the reaction of ICH_2Bnor over terminal alkenes (NMR yields)

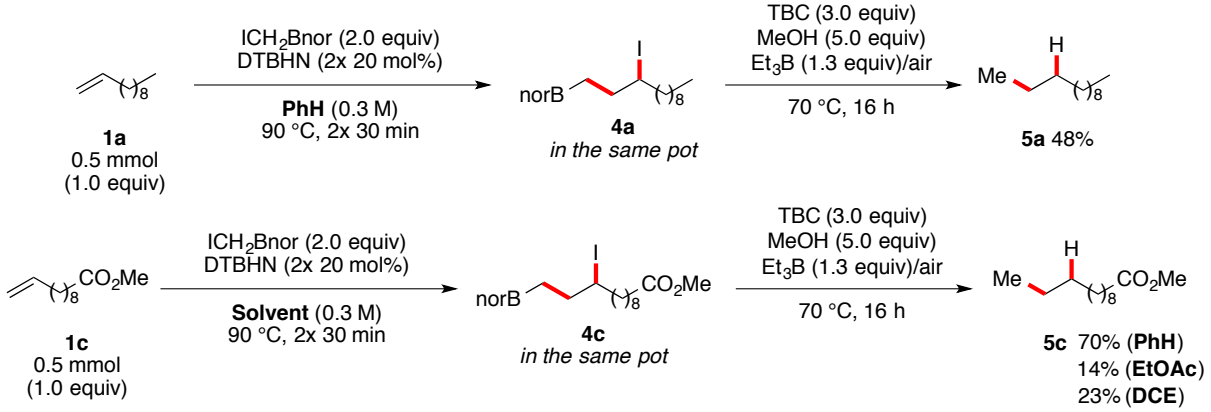
3.5.2 One-pot sequence – Initial investigations

Next, we examined the feasibility of a one-pot sequence involving i) the DTBHN–initiated ATRA reaction in refluxing ethyl acetate, ii) a solvent switch to benzene, iii) the deiodination and protodeboronation process. The solvent switch was done with or without inert protection (Schlenk or rotary evaporator) to subsequently engage the resulting crude residue to the one-pot deiodination/protodeboronation sequence (Scheme 26). In practice, this approach proved low yielding. Partial decomposition of the ATRA product may occur during solvent evaporation (e.g., formation of hydrogen iodide (HI) which can catalyze further the decomposition of the ATRA product) (Scheme 26). Surprisingly, when decomposition of the ATRA product was prevented by mean of an aqueous work-up, only traces of hydromethylated product **5a** were obtained.



Scheme 26. Investigations on a hydromethylation sequence involving a solvent switch between DTBHN–initiated ATRA and deiodination/protodeboronation processes (GC yields)

Considering the difficulties encountered with the solvent switch strategy, we tested the one-pot sequence in benzene as a unique solvent for the three processes. Alkenes **1a** and **1c** were selected as a result of their established good reactivity in the DTBHN–initiated ATRA process (Scheme 27). In both cases, we were pleased to observe that by using benzene, **5a** and **5c** were obtained in moderate to satisfactory yields. As expected, when ethyl acetate was employed in the deiodination/protodeboronation process, the hydromethylated product **5c** was obtained in poor yields, highlighting the incompatibility of the reaction conditions with Lewis base solvents. Surprisingly, DCE did not proved to be suitable neither.

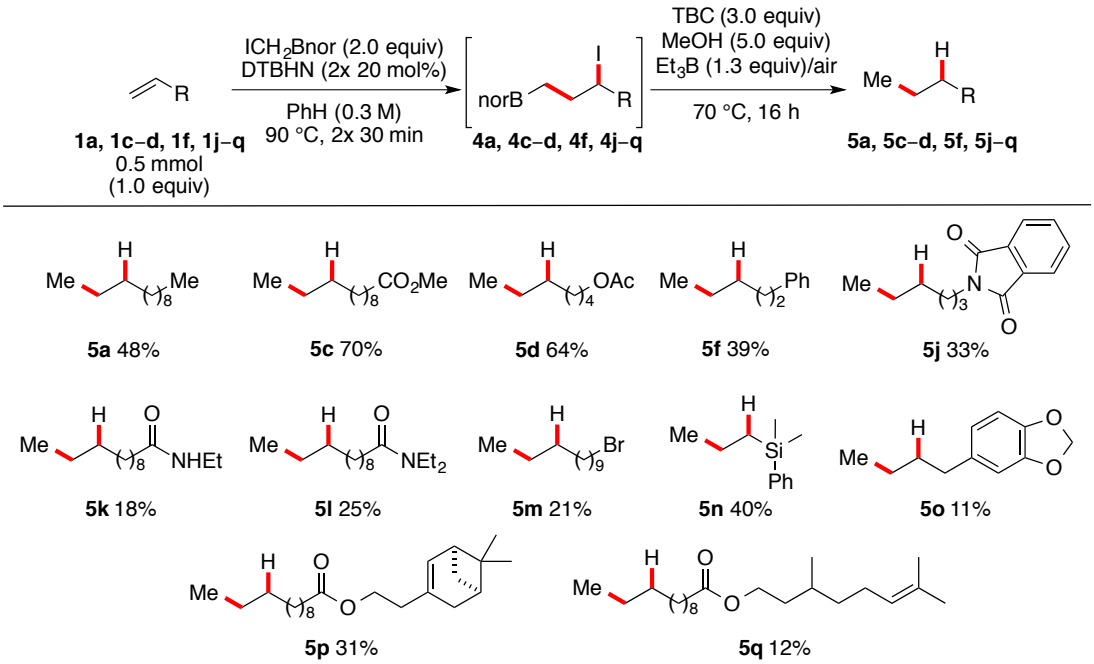


Scheme 27. Solvent screening for the hydromethylation sequence (GC yields)

3.5.3 Scope of the hydromethylation sequence

Moving forward, we started to explore the substrate scope of this hydromethylation sequence (Scheme 28). For most of the substrates, GC yields were performed but isolation of the hydromethylated product can be done in a straightforward manner. Terminal alkenes bearing an ester or an acetate were well tolerated as shown by the synthesis of **5c** and **5d**. In contrast to the abovementioned hydromethylation sequence, the silane **5n** and the phenyl **5f** were accessed in moderate yields. When the secondary and tertiary amide derivatives **5k** and **5l** were subjected to the sequence, poor yields were detected, presumably as a result of the inefficient DTBHN–initiated ATRA process in benzene (Scheme 24, **4l**). As described for the DLP–initiating methodology, substrates **1j**, **1m** and **1o** proved to be incompatible with the hydromethylation reaction conditions. Eventually, the chemoselective hydromethylation of dienes **1p**–**q** was studied and resulted in poor yields. Hence, this method has currently defined

limitations and would require more investigations on the DTBHN–initiated ATRA process. Importantly, the inability to perform the protodeboronation/deiodination process on the crude ATRA residue after work-up needs to be understood. If solved, a solvent switch approach could readily improve the efficient of the overall transformation.



Scheme 28. Scope of the hydromethylation sequence (GC yields)

3.6 Conclusion

In summary, we have developed a synthetically useful procedure for the formal anti-Markovnikov hydromethylation of unactivated alkenes. We were able to carry out a one-pot sequence combining an ATRA process that enables the regioselective insertion of a C1-synthon, and a simultaneous deiodination and protodeboronation protocol. As an alternative to the initiation of the ATRA process with DLP, DTBHN initiation has been investigated and promising results were obtained although further optimizations need to be undertaken to attain satisfying yields over the one-pot protocol. A stepwise approach involving i) an ATRA process, ii) a deiodination and iii) a protodeboronation reaction is currently investigated by Gaetano Geraci. This sequential transformation will prove particularly useful to access homologated boronic ester (i.e. after ATRA and deiodination) and will enable the use of milder reaction conditions compared to the well-known Matteson homologation.

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Experimental Part

Contents

1. General and instrumentation

Glassware and reaction techniques: Unless otherwise stated, all glassware was flame-dried, cooled under vacuum, and back-filled with nitrogen or argon; then the reactions were run under that inert atmosphere (atm) and additions of solids were performed under a positive pressure of that inert atm. Unless otherwise stated, all yields are isolated yields. Room temperatures (rt) were generally in the range 21–25 °C.

Solvents: Tetrahydrofuran (THF), diethyl ether (Et_2O), hexane, and benzene (PhH) for reactions were filtered through a column of dried alumina under a positive pressure of argon. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. All water used for solutions, quenches, and aqueous extractions was deionized water.

Reagents and chemicals: All reagents and chemicals used were commercial and used without further purification unless specified below.

Column chromatography: All chromatographic purifications were flash (ca. 2–3 atm of pressurized air) column chromatography (FCC) on silica gel (Macherey-Nagel Silica 60, 0.04 – 0.063 mm) and/or neutral aluminium oxide (CAMAG 507 – C – I neutral).

Thin layer chromatography (TLC): Silicycle glass backed TLC extra hard layer, 259 µm, 60 Å, F-254 Silica gel 60 Å (F-254) and *Macherey-Nagel* SIL G/UV254, 0.25 mm analytical plates were used for TLC. Revelation was done firstly by non-destructive visualization under a UV lamp (254 nm); destructive revelation was performed with staining solutions of either potassium permanganate ($KMnO_4$), cerium molybdate (CAM), or cerium sulfate ($Ce(SO_4)_2$), followed by heating.

NMR: The NMR experiments were performed on a Bruker Avance-300 spectrometer operating at a resonance frequency of 300.18 MHz for ^{1}H nuclei, 75.48 MHz for ^{13}C and 96 MHz for ^{11}B nuclei. ^{11}B NMR spectra were calibrated using $Et_2O.BF_3$ (0.0 ppm) as an external reference. Chemical shifts are reported in units of δ (ppm) using the internal standard residual $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR spectra and δ = 77.16 ppm for ^{13}C NMR spectra), or DMSO-d6 (δ = 2.50 ppm for ^{1}H NMR spectra and δ = 39.52 ppm for ^{13}C NMR spectra), or TMS (δ = 0.00 ppm for ^{1}H NMR spectra and δ = 0.00 ppm for ^{13}C NMR spectra). Due to coupling to the quadrupolar ^{11}B and ^{10}B nuclei, the carbons linked to boron atoms generally give a broad signal in ^{13}C NMR and are usually not detectable. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextuplet, m =

multiplet, app = apparent. Referencing and common impurities were assigned by common standards.[1,2]

Procedure for the determination of yields by ^1H NMR: NMR yields were determined using 1,4-dimethoxybenzene (s, 6.74 ppm, 4H; s, 3.67 ppm, 6H) as an internal standard. The standard was added to the crude residue after aqueous work-up, dissolved in $CDCl_3$ by swirling and sonicated for 5 mins in order to have a homogenous mixture. An aliquot was transferred in a NMR tube and analyzed by ^1H NMR.

GC: GC analyses were carried out on a Thermo Electron Trace GC ULTRA instrument fitted with a Macherey-Nagel Optima delta-3-0.25 μm capillary column (20 m, 0.25 mm). Gas carrier: He 1.4 mL/min; injector: 220 °C split mode; detector: FID 280 °C, H2 35 mL/min, air 350 mL/min. Infrared spectra were recorded on a Jasco FT/IR-4700 Spectrometer and are reported in wave numbers (cm^{-1}).

Procedure for the determination of yields by GC analysis: an internal standard (typically 0.5 equivalent) was added along with substrates and reagents. After reaction, an aliquot was added to a mixture of EtOAc and 1.0 M aq. NaOH. The organic phase was washed with sat. aq. $NaHCO_3$ and then filtered over a small pad of Na_2SO_4 and neutral aluminium oxide (ca. 0.5 cm of Na_2SO_4 and 1 cm of neutral aluminium oxide in a Pasteur pipette and eluted with EtOAc). The resulting sample was injected in GC using the method described above.

MS: HRMS analyses and elemental composition determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using ESI and NSI mode at the University of Bern. When ESI and NSI was not sufficient to ionize the molecule, HRMS was performed at the University of Zürich with a Bruker maXis QTof high resolution mass spectrometer (APCI mode) and Thermo DFS (ThermoFisher Scientific) double-focusing magnetic sector mass spectrometer (EI and CI modes).

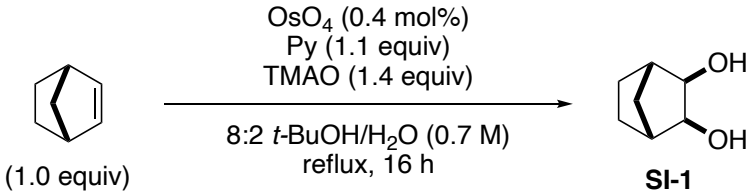
IR: Infrared spectra were recorded neat equipped with a diamond ATR System and are reported in wave numbers (cm^{-1}). Reported are the characteristic signals only (with decreasing wave number).

*Compounds **1a–b**, **1d**, **1f–g**, **1j** and **1m–o** were commercially available and used as such. Compounds **5a–d**, **5f**, **5i**, **5l–m**, **5o**, **5aa** and **6a** were purchased and used as references for GC yield determinations. Compounds **SI-1**, ICH_2Bnor, **1c**, **1e**, **1k–l**, and **1p–r** were provided by Dr. Tappin, and synthetized following reported conditions,[3,4] and compounds **SI-1**, ICH_2Bnor were resynthesized as described herein. The characterizations and spectral data of compounds **4a–g**,*

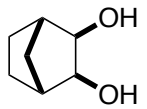
3a–b *and* ***3d*** *were also provided by Dr. Tappin who has investigated ATRA and deiodination processes.*

2. Experimental Procedures and Characterizations for the Synthesis of Reagents and Substrates

2.1 Dihydroxylation of norbornene



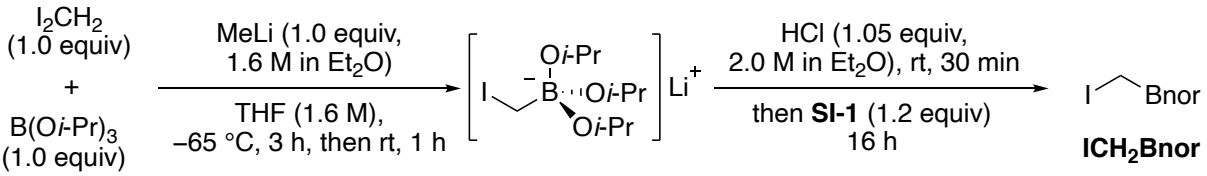
exo-Bicyclo[2.2.1]heptane-2,3-diol (SI-1)



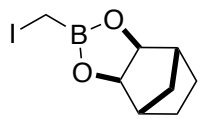
$C_7H_{12}O_2$
MW: 128.08

To a one-neck, 2 L round-bottom flask was added trimethylamine N-oxide dihydrate, TMAO.2H_2O (78.0 g, 700 mmol, 1.4 equiv), *t*-BuOH (640 mL), H_2O (160 mL) (8:2, 0.7 M), pyridine (44.5 mL, 550 mmol, 1.1 equiv), norbornene (48.0 g, 500 mmol, 1.0 equiv) and osmium tetroxide, OsO_4 (500 mg, 2.00 mmol, 0.4 mol%, entire sealed ampoule). The reaction mixture was heated under a gentle reflux (80 °C) for 16 h. The volatiles were removed *in vacuo* (caution: perform in a well-ventilated fume-hood). The residue was diluted with EtOAc and washed twice with 2.0 M HCl. The aqueous phase was back-extracted twice with EtOAc. The combined ethereal phases were washed twice with sat. aq. $Na_2S_2O_3$, once with sat. aq. $NaHCO_3$, dried with sat. aq. NaCl, then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was diluted with CH_2Cl_2, filtered through a plug of SiO_2 (washed with CH_2Cl_2), and concentrated *in vacuo*. The crude was crystallized from heptanes and recrystallized from heptanes to afford **SI-1** as a fine white crystal (44.4 g, 350 mmol, 69%). Spectral and physical data were in accordance with the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 2H), 3.57 (s, 2H), 2.10 (dq, *J* = 3.3, 1.6 Hz, 2H), 1.72 (dp, *J* = 10.4, 2.1 Hz, 1H), 1.52 – 1.33 (m, 2H), 1.07 (dq, *J* = 10.3, 1.4 Hz, 1H), 1.04 – 0.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.8, 43.1, 31.7, 24.6.

2.2 Synthesis of iodide radical precursor ICH_2Bnor



***exo*-2-(Iodomethyl)hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborole (ICH_2Bnor)**



$C_8H_{12}BIO_2$
MW: 278.00

A three-neck, 250 mL round-bottom flask equipped with a 100 mL dropping funnel and a low-temperature thermometer was charged with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, B(O*i*-Pr)$_3$ (23.0 mL, 100 mmol, 1.0 equiv), diiodomethane, I_2CH_2 (8.12 mL, 100 mmol, 1.0 equiv) and THF (56 mL, 1.6 M) and dissolved with vigorous stirring. Methyllithium (1.6 M in Et_2O, 62 mL, 100 mmol, 1.0 equiv) was loaded into the dropping funnel via cannula. The contents of the flask were cooled to –78 °C with a dry ice/acetone bath and the MeLi solution was added at a steady strip rate to maintain the temperature below –65 °C, over approximately 3 h. Once addition was completed the reaction mixture was stirred at this temperature for a further hour and the cooling bath removed. Dry HCl (52 mL, 2.0 M in Et_2O, 1.05 equiv) was added quickly at no particular temperature. The flask was stirred for a further hour at rt, and **SI-1** (13.4 g, 120 mmol, 1.2 equiv) was added quickly. The contents were stirred at rt for 16 h, and the majority of the volatiles were removed *in vacuo* (caution: MeI – perform in a well-ventilated fume-hood). The remaining contents were partitioned between TBME (50 mL) and 10% (w/v) aq. $Na_2S_2O_3$ (50 mL) and stirred for five minutes. The organic phase was washed with water (100 mL), sat. aq. $NaHCO_3$ (100 mL), dried with sat. aq. NaCl (100 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was vacuum distilled (100 – 110 °C, 4.2×10^{-2} mbar) to afford **ICH_2Bnor** as a pale-yellow oil (13.8 g, 49.8 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, *J* = 1.1 Hz, 2H), 2.33 (dq, *J* = 3.1, 1.5 Hz, 2H), 2.19 (s, 2H), 1.71 (ddt, *J* = 11.1, 3.8, 2.1 Hz, 1H), 1.50 (dtd, *J* = 8.3, 6.1, 3.3 Hz, 2H), 1.25 (dp, *J* = 11.0, 1.3 Hz, 1H), 1.08 – 1.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.4, 41.0, 30.8, 23.4. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.2. IR (neat): 2959, 1386, 1306, 1280, 1225, 1022, 1001, 828 cm^{-1}. HRMS (ESI) calcd. for $C_8H_{12}BIO_2$ $[M]^+$: 277.9970; found: 277.9961.

2.3 Synthesis of DTBHN and MeOBcat

Di-*tert*-butyl hyponitrite (DTBHN)

t-BuON=NO*t*-Bu
$C_8H_{18}N_2O_2$
MW: 174.24

DTBHN was prepared according to a slightly altered literature procedure.[6] In a 250 mL three-neck flask equipped with a stirring bar was loaded sodium *trans*-hyponitrite hydrate (8.15 g) which was then dried to constant weight (5.58 g). In another flask, $ZnCl_2$ hydrate (14 g) was melted under stirring *in vacuo* (thrice) in order to dry it. From the resulting block of grey solid, pieces with a total weight of 8.6 g (63.1 mmol, 1.2 equiv) were (quickly) transferred into a two-neck flask, dried another 10 min under vacuum, and then suspended in Et_2O (35 mL) first with stirring for 2 h then with sonication for another 20 min until no more pieces of $ZnCl_2$ were visible. To the dry hyponitrite was added Et_2O (30 mL) and *tert*-butylbromide (47 mL, 418 mmol, 8.0 equiv) and the resulting milky white mixture was cooled to –10 °C (internal temperature) using an ice/NaCl/water bath. Then, the $ZnCl_2$ suspension was transferred into the reaction vessel with the hyponitrite using a cannula (Ø = 1 mm) at a rate that the internal temperature did not exceed –5 °C. After complete addition, the mixture was allowed to reach rt and stirred for another 1.5 h at this temperature. The reaction mixture was filtered and the remaining solid was washed with Et_2O (3×10 mL). The resulting yellow solution was transferred into a separatory funnel and water was added. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and the volatiles were removed under reduced pressure (bath temperature 20 °C, 400 mbar, end to 50 mbar for a short time). The obtained solid was crystallized from *n*-pentane to furnish almost colorless crystals in three crops (all crops were washed with cold pentane). Recrystallization from pentane of the combined crops furnished the product as colorless, transparent crystals (3.43 g, 37%). DTBHN was stored for months at 4 °C. Spectral and physical data were in accordance with the literature.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.2, 27.8.

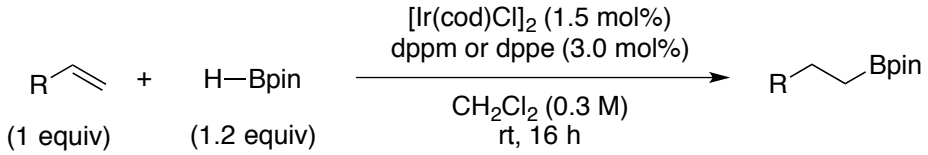
2-Methoxybenzo[*d*][1,3,2]dioxaborole (MeOBcat)

MeOBcat
$C_7H_7BO_3$
MW: 150.05

A one-neck, 100 mL round-bottom flask was charged with catecholborane (4.0 mL, 37.5 mmol, 1.0 equiv) and benzene (25 mL, 1.5 M). MeOH (1.52 mL, 37.5 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred at rt until no more H_2 evolution was visible (around 1 h). The solvent was removed under reduced pressure and the residue was vacuum distilled (44 °C, 4×10^{-2} mbar) to afford MeOBcat as a colorless oil (3.2 g, 21.1 mmol, 57%). Spectral and physical data were in accordance with the literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.59 (m, 2H), 6.48 – 6.42

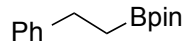
(m, 2H), 3.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 121.1, 110.8, 51.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 23.4.

2.4 General Procedure 1 (GP1): Iridium catalyzed hydroboration of terminal alkenes to furnish 2h and 2i[9]



A one-neck, 250 mL round-bottom flask was charged with $[Ir(cod)Cl]_2$ (1.5 mol%) and ethylenebis(diphenylphosphine) (dppe) or methylenebis(diphenylphosphine) (dppm) (3 mol%) in a glove-box. CH_2Cl_2 (3 mL/mmol), pinacolborane (1.2 equiv), and the alkene (1 equiv) were added successively to the flask at 0 °C, and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched with MeOH (1 mL/mmol) and H_2O (3 mL/mmol) and the aqueous phase was extracted with CH_2Cl_2 (2×4 mL/mmol). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude residue.

4,4,5,5-Tetramethyl-2-(2-phenylethyl)-1,3,2-dioxaborolane (2h)



$C_{14}H_{21}BO_2$
MW: 232.16

From styrene (5.21 g, 50.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **2h** as a colorless liquid (10.94 g, 47.1 mmol, 84%). Spectral and physical data were in accordance with the literature.[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.13 (m, 5H), 2.75 (dd, $J_A = J_B$ = 8.2 Hz, 2H), 1.22 (s, 12H), 1.15 (dd, $J_A = J_B$ = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 128.3, 128.1, 125.6, 83.2, 30.1, 25.0. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.8.

4,4,5,5-Tetramethyl-2-octyl-1,3,2-dioxaborolane (2i)

n-octBpin

$C_{14}H_{29}BO_2$
MW: 240.23

From 1-octene (4.50 g, 40.0 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **2i** as a colorless oil (8.94 g, 37.2 mmol, 93%). Spectral and physical data were in accordance with the literature.[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 – 1.38 (m, 2H), 1.32

– 1.24 (m, 22H), 0.89 – 0.85 (m, 3H), 0.77 (app t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.8, 32.5, 31.9, 29.4, 29.3, 24.8, 24.0, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.1.

3. General Experimental Procedures for the ATRA reactions

3.1 General Procedure 2 (GP2): I-ATRA initiated with DLP

A one-neck, 10 mL round-bottom flask, equipped with a cold-finger condenser, was charged with alkene **1a–g** (1.0 mmol), **ICH$_2$Bnor** (695 mg, 2.5 mmol), dilauroyl peroxide, DLP (1.0 mmol, 398 mg), and the contents dissolved in benzene (3.3 mL, 0.3 M) under an Ar atm. The reaction mixture was heated at a gentle reflux for 4 h (oil-bath temperature set to 90 °C). The cooled reaction solution was partitioned between TBME (15 mL) and H_2O (10 mL) and shaken with sat. aq. $Na_2S_2O_3$ (5 mL). The ethereal phase was washed with water (10 mL), and the combined aqueous phases was back-extracted with TBME (5 mL). The combined ethereal phases was washed with sat. aq. $NaHCO_3$ (2×15 mL), dried with sat. aq. NaCl (15 mL), then dried over Na_2SO_4, filtered through a short pad of silica-gel ($Ø_{int}$ = 15 mm, l = 2 cm), and concentrated *in vacuo*. The crude residue was submitted to purification by FCC (silica-gel; $Ø_{int}$ = 45 mm; l = 20 cm; collection tube volume = 25–50 mL; eluent reservoir volume = 250 mL; elution gradient reported in discrete increments according to eluent reservoir volume).

3.2 General Procedure 3 (GP3): I-ATRA initiated with DTBHN

A one-neck, 10 mL round-bottom flask, equipped with a cold-finger condenser, was charged with alkene **1a**, **1c–d**, **1l** (1.0 mmol) and **ICH$_2$Bnor** (695 mg, 2.5 mmol), and the contents dissolved in EtOAc (3.3 mL, 0.3 M) under a normal atm. DTBHN (35 mg, 0.2 mmol) was added to the reaction solution quickly in one portion, the reaction flask was immediately immersed in a pre-heated oil bath set to 90 °C, and the reaction solution was heated at reflux for 30 min. The flask was raised from the oil bath, allowed to cool, another portion of DTBHN (35 mg, 0.2 mmol) was added, and then the flask was immersed again in the oil bath for a

further 30 min. The contents were concentrated *in vacuo* and the crude residue was submitted to purification by FCC (silica-gel; $Ø_{int}$ = 25 mm; l = 20 cm; collection tube volume = 20 mL; eluent reservoir volume = 100 mL; elution gradient reported in discrete increments according to eluent reservoir volume). When acid-sensitive functional groups were present on the substrate, product yields generally benefitted from an aqueous work-up as described in **GP2**. *For NMR yields* (**1a**, **1c–d**, **1l**): see protocol described in "General and instrumentation".

4. General Experimental Procedures for the ATRA/ deiodination sequence

4.1 General Procedure 4 (GP4): I-ATRA initiated with DLP and subsequent deiodination using Barton's conditions

A one-neck, 25 mL round-bottom flask equipped with a condenser was charged with **ICH_2Bnor** (2.0 equiv), dilauroyl peroxide, DLP (1.0 equiv), **1a–b**, **1d** (1.0 equiv) and benzene or EtOAc (0.3 M) under a positive pressure of N_2 atm, then heated under reflux for 4 h. At the end of the ATRA sequence the cooled reaction flask was charged with hypophosphorous acid, H_3PO_2 (10.0 equiv, 50 w% in water), Et_3N (11.0 equiv, distilled prior to use), AIBN (20 mol%), and either dioxane (2 mL) or MeCN (2 mL), and the contents were heated at 90 °C for 1.5 h. After partial cooling, another portion of AIBN (20 mol%) was added and the contents heated at 90 °C for a further 1.5 h. The contents were cooled to rt, partitioned between TBME (25 mL) and 2 M aq. HCl (15 mL). The ethereal phase was washed with 1 M aq. HCl (15 mL), and the combined aqueous phases was back-extracted with TBME (5 mL). The combined ethereal phases were washed with 2 M aq. NaOH (15 mL) and 1 M aq. NaOH (15 mL), then shaken with sat. aq. $Na_2S_2O_3$ (25 mL). The ethereal phase was washed sat. aq. $NaHCO_3$ (25 mL), dried with sat. aq. NaCl (25 mL), then dried over Na_2SO_4, filtered over a short pad of silica, and concentrated *in vacuo*.

5. General Experimental Procedures for the one-pot hydromethylation sequence

5.1 General Procedure 5 (GP5): Hydromethylation sequence with I-ATRA initiated with DLP

A one-neck, 10 mL round-bottom flask equipped with a condenser was charged with **ICH$_2$Bnor** (2.0 equiv), dilauroyl peroxide, DLP (1.0 equiv), **1a–b**, **1d**, **1f**, **1j–r** (1.0 equiv) and benzene or EtOAc (0.3 M) under a positive pressure of N_2 atm, then heated under reflux for 4 h. The reaction mixture was cooled to rt and *tert*-butyl catechol, TBC (3.0 equiv), MeOH (5.0 equiv) and triethylborane, Et_3B (2 M in PhH, 1.3 equiv) were added in sequence. The resulting mixture was heated at 70 °C for 16 h, open to air. *For isolation* (**5a** and **5d**): The contents were cooled to rt, partitioned between TBME (10 mL) and H_2O (10 mL) and shaken with sat. aq. $Na_2S_2O_3$ (10 mL). The ethereal phase was washed with water (10 mL), and the combined aqueous phases were back-extracted with TBME (10 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$ (10 mL), dried with sat. aq. NaCl (10 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. *For GC yields* (**5a-b**, **5d**, **5f**, **5j-q**): see protocol described in "General and instrumentation" and chromatograms in "9. GC chromatograms".

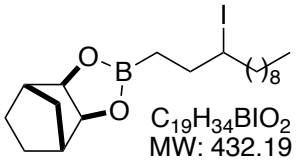
5.2 General Procedure 6 (GP6): Hydromethylation sequence with I-ATRA initiated with DTBHN

A one-neck, 10 mL round-bottom flask equipped with a condenser was charged with **ICH$_2$Bnor** (2.0 equiv), **1a**, **1c–d**, **1f**, **1j–q** (1.0 equiv), benzene or EtOAc (0.3 M) and DTBHN (20 mol%) under a positive pressure of N_2 atm. The reaction flask was immersed in a pre-heated oil bath (90 °C) and heated under reflux for 30 min. In cases when TLC indicated poor conversion, another portion of DTBHN (20 mol%) was added and the contents were heated under reflux for a further 30 min. The reaction mixture was cooled to rt and *tert*-butyl catechol, TBC (3.0 equiv), MeOH (5.0 equiv) and triethylborane, Et_3B (2 M in PhH, 1.3 equiv) were added in sequence. The resulting mixture was heated at 70 °C for 16 h, open to air. *For GC yields* (**5a**, **5c–d**, **5f**, **5j–q**): see protocol described in "General and instrumentation".

6. Experimental procedures and characterizations for the synthesis of ATRA compounds

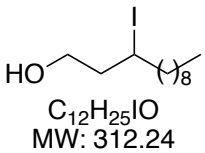
6.1 Synthesis of 4a–g following GP2.

exo-2-(3-Iodododecyl)hexahydro-4,7-methanobenzo[_d_][1,3,2]dioxaborole (4a)



From 1-undecene (0.43 mL, 2.0 mmol), ICH_2Bnor (1.11 g, 4.0 mmol, 2.0 equiv), and dilauroyl peroxide (0.75 g, 2.0 mmol) in benzene (6.5 mL, 0.3 M), using a one-neck, 25 mL round-bottom flask (**GP2**). The crude residue was submitted to purification by FCC (grad = 0.5-0.5-1-1% EtOAc/heptanes) to afford 4a as a pale orange oil (769 mg, 1.78 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (br d, J = 1.3 Hz, 2H), 4.18 – 4.08 (m, 1H), 2.26 (m, 2H), 2.00 – 1.78 (m, 3H), 1.78 – 1.63 (m, 1H), 1.57 – 1.43 (m, 4H), 1.35 – 1.23 (m, 13H), 1.19 (dt, J = 11.1, 1.4 Hz, 1H), 1.09 – 0.99 (m, 3H), 0.95 (dd, J = 10.2, 6.3 Hz, 1H), 0.92 – 0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.7, 43.8, 40.9, 40.3, 35.2, 31.9, 30.7, 29.6, 29.50, 29.48, 29.3, 28.9, 23.3, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9. IR (neat): 2954, 2922, 2873, 2852, 1386, 1370, 1321, 1310, 1283, 1224, 1166, 1132, 1028 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{34}O_2BINa$ $[M+Na]^+$: 455.1589; found: 455.1583.

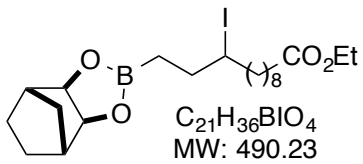
3-Iodododecan-1-ol (SI-2)



*A clean isolation of the 3-iodoboronic ester **4a** could not be accomplished when it was synthesized using **GP2**. However, the organoboron compound could be oxidized to the primary alcohol **SI-2** in a two-step sequence by treatment with $NaBO_3$.* The general procedure **GP2** was followed on a 3.0 mmol scale, i.e., in a 25 mL flask with 1-undecene (0.63 mL, 3.0 mmol), ICH_2Bnor (1.83 g, 6.6 mmol, 2.2 equiv), and dilauroyl peroxide (1.19 g, 3.0 mmol) in benzene (10 mL, 0.3 M). The crude residue was submitted to FCC purification (silica-gel; $Ø_{int}$ = 55 mm; l = 23 cm; collection tube volume = 100 mL; eluent reservoir volume = 500 mL; elution gradient reported in discrete increments according to eluent reservoir volume, grad = 0.5-1-1-2-2-2% EtOAc/heptanes). The impure product **4a** [R_f = 0.39 (8% EtOAc/heptanes, CAM, UV)] was submitted to an oxidative treatment. To a one-neck (NS 29/32) 100 mL, round-bottom flask, with large stir bar, was loaded the impure 3-iodoboronic ester **4a**, sodium perborate tetrahydrate (5.1 g, 33.0 mmol (5.0 equiv per mmol of C—B bonds)), THF (30 mL), and H_2O (30 mL). The reaction mixture was

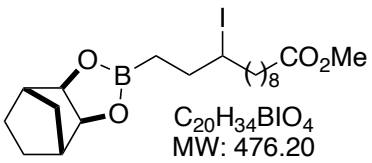
stirred vigorously overnight at rt with intermittent heat gun heating to disperse clumps of the perborate salts. The majority of volatiles were removed *in vacuo*. The residue was partitioned between TBME (40 mL) and 2 M aq. HCl (25 mL) and the ethereal phase was washed with 1 M aq. HCl (2×25 mL) and the combined aqueous phases was back-extracted with TBME (10 mL). The combined ethereal phases was washed with sat. aq. $NaHCO_3$ (50 mL) followed by sat. aq. NaCl (50 mL). The ethereal phase was dried over Na_2SO_4, filtered through a silica plug ($Ø_{int}$ = 15 mm, l = 2 cm), and concentrated *in vacuo*. The crude residue was submitted to FCC purification (grad = 3-4-5-7-10-15% EtOAc/heptanes) to afford **SI-2** as a clear oil (527 mg, 1.69 mmol, 56% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (dq, *J* = 13.6, 4.4 Hz, 1H), 3.81 (m, 2H), 2.18 – 1.83 (m, 3H), 1.74 (ddt, *J* = 14.5, 10.1, 4.9 Hz, 1H), 1.60 – 1.48 (m, 2H), 1.46 – 1.38 (m, 1H), 1.38 – 1.18 (m, 12H), 0.88 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.6, 42.7, 40.9, 35.8, 31.9, 29.53, 29.50, 29.49, 29.3, 28.8, 22.7, 14.1. IR (neat): 3308, 2922, 2852, 1464, 1377, 1144, 1044, 721 cm^{-1}. **SI-2** (from step 2): HRMS (ESI) calcd. for $C_{12}H_{26}OI$ $[M+H]^+$: 313.1023; not found. **4a** (from step 1): HRMS (ESI) calcd. for $C_{19}H_{35}O_2BI$ $[M+Na]^+$: 455.1589; found: 455.1583.

Ethyl *exo*-12-(hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-10-iodododecanoate (4b)



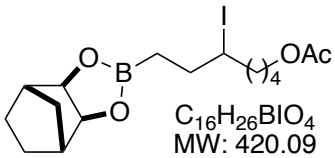
From ethyl undec-10-enoate (0.29 mL, 2.0 mmol), ICH_2Bnor (1.11 g, 4.0 mmol, 2.0 equiv), and dilauroyl peroxide (0.75 g, 2.0 mmol) in benzene (6.5 mL, 0.3 M), using a one-neck, 25 mL round-bottom flask (**GP2**). The crude residue was submitted to FCC purification (grad = 2-3-4-5% EtOAc/heptanes) to afford **4b** as a pale orange oil (665 mg, 1.36 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (app br d, *J* = 1.4 Hz, 2H), 4.18 – 4.07 (m, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 2.34 – 2.23 (m, 4H), 2.02 – 1.77 (m, 3H), 1.77 – 1.57 (m, 3H), 1.57 – 1.44 (m, 4H), 1.36 – 1.27 (m, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19 (app br dt, *J* = 11.0, 1.4 Hz, 1H), 1.12 – 0.99 (m, 3H), 0.95 (app dd, *J* = 10.2, 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 83.7, 60.1, 43.7, 40.9, 40.3, 35.2, 34.4, 30.7, 29.5, 29.3, 29.2, 29.1, 28.8, 25.0, 23.3, 14.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9. IR (neat): 1733 cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{21}H_{37}O_4BI$ $[M+H]^+$: 491.1824; found: 491.1803.

Methyl *exo*-12-(hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-10-iodododecanoate (4c)



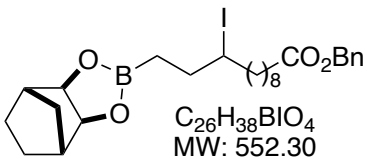
From methyl undec-10-enoate (0.23 mL, 1.0 mmol) following **GP2**. The crude residue was submitted to FCC purification (grad = 2-3-4-5% EtOAc/heptanes) to afford **4c** as a clear oil (342 mg, 0.718 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, *J* = 1.4 Hz, 2H), 4.13 (tt, *J* = 8.6, 4.7 Hz, 1H), 3.67 (s, 3H), 2.30 (app t, *J* = 7.6 Hz, 2H), 2.26 (m, 2H), 2.00 – 1.76 (m, 3H), 1.76 – 1.57 (m, 3H), 1.57 – 1.45 (m, 4H), 1.37 – 1.24 (m, 9H), 1.19 (app dp, *J* = 11.0, 1.4 Hz, 1H), 1.08 – 0.99 (m, 3H), 0.95 (dd, *J* = 10.2, 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 83.7, 51.4, 43.7, 40.9, 40.3, 35.2, 34.1, 30.7, 29.4, 29.24, 29.17, 29.1, 28.8, 24.9, 23.3, 10.7 (br w, α-boryl-CH_2, broadened and almost lost in the baseline noise due to quadrupolar couplings to ^{11}B and ^{10}B). ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.8. IR (neat): 1738 cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{20}H_{35}O_4BI$ $[M+H]^+$: 477.1668; found: 477.1649.

***exo*-7-(Hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-5-iodoheptyl acetate (4d)**



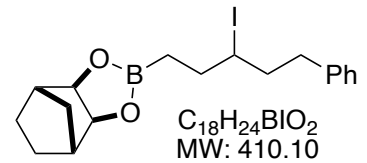
From 5-hexenyl acetate (0.33 mL, 2.0 mmol), ICH_2Bnor (1.11 g, 4.0 mmol, 2.0 equiv), and dilauroyl peroxide (0.75 g, 2.0 mmol) in benzene (6.5 mL, 0.3 M), using a one-neck, 25 mL round-bottom flask (**GP2**). The crude residue was submitted to FCC purification (silica-gel; $Ø_{int}$ = 55 mm; l = 23 cm; collection tube volume = 50 mL; eluent reservoir volume = 250 mL; elution gradient reported in discrete increments according to eluent reservoir volume, grad = 2-2-3-5-10% EtOAc/heptanes) to afford **4d** as a clear oil (649 mg, 1.55 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (app br d, *J* = 1.4 Hz, 2H), 4.12 (m, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 2.26 (m, 2H), 2.05 (s, 3H), 1.98 – 1.71 (m, 4H), 1.71 – 1.53 (m, 4H), 1.53 – 1.44 (m, 3H), 1.19 (app dt, *J* = 11.0, 1.4 Hz, 1H), 1.09 – 1.00 (m, 3H), 0.95 (app dd, *J* = 10.1, 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 83.9, 64.4, 42.9, 41.00, 39.97, 35.4, 30.8, 28.0, 26.2, 23.5, 21.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.5. IR (neat): 1736 cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{16}H_{27}O_4BI$ $[M+H]^+$: 421.1042; found: 421.1038.

Benzyl *exo*-12-(hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-10-iodododecanoate (4e)



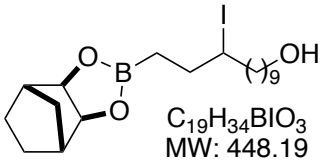
From benzyl undec-10-enoate (552 mg, 1.0 mmol) following **GP2**. The crude residue was submitted to FCC purification (grad = 2-3-4-5% EtOAc/heptanes) to afford **4e** as a pale orange oil (361 mg, 0.654 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.11 (s, 2H), 4.20 (app br d, *J* = 1.3 Hz, 2H), 4.13 (tt, *J* = 8.7, 4.7 Hz, 1H), 2.35 (app t, *J* = 7.5 Hz, 2H), 2.26 (app br dq, *J* = 3.4, 1.6 Hz, 2H), 2.01 – 1.76 (m, 3H), 1.73 – 1.58 (m, 3H), 1.56 – 1.44 (m, 4H), 1.36 – 1.23 (m, 9H), 1.19 (app br dp, *J* = 11.0, 1.4 Hz, 1H), 1.12 – 1.00 (m, 3H), 0.95 (app dd, *J* = 10.2, 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 136.1, 128.5, 128.16, 128.15, 83.7, 66.1, 43.7, 40.9, 40.3, 35.2, 34.3, 30.7, 29.4, 29.25, 29.16, 29.07, 28.8, 24.9, 23.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.8. IR (neat): 1734 (s) cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{26}H_{39}O_4BI$ $[M+H]^+$: 553.1981; found: 553.1972.

***exo*-2-(3-Iodo-5-phenylpentyl)hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborole (4f)**



From but-3-en-1-ylbenzene (0.15 mL, 1.0 mmol) following **GP2**. The crude residue was submitted to FCC purification (grad = 1-2-2-3-4% EtOAc/heptanes) to afford 306 mg of impure product. A second FCC (1% EtOAc/heptanes) afforded pure **4f** as a clear oil (244 mg, 0.60 mmol, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 4.18 (d, *J* = 1.3 Hz, 2H), 4.07 (tt, *J* = 8.8, 4.4 Hz, 1H), 2.88 (ddd, *J* = 14.0, 9.1, 5.1 Hz, 1H, as half of ABq), 2.72 (ddd, *J* = 13.7, 9.0, 6.9 Hz, 1H, as half of ABq), 2.24 (m, 2H), 2.21 – 2.07 (m, 1H), 2.05 – 1.91 (m, 2H), 1.90 – 1.76 (m, 1H), 1.52 – 1.41 (m, 3H), 1.17 (dt, *J* = 11.0, 1.4 Hz, 1H), 1.12 – 0.81 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 128.5, 128.4, 126.0, 83.7, 42.4, 41.9, 40.8, 35.6, 35.3, 30.7, 23.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9. IR (neat): 2950, 2922, 2874, 1495, 1454, 1386, 1369, 1321, 1284, 1223, 1132, 1105, 1026, 1002 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{25}O_2BI$ $[M+H]^+$: 411.0987; found: 411.0983.

***exo*-12-(Hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-10-iodododecan-1-ol (4g)**

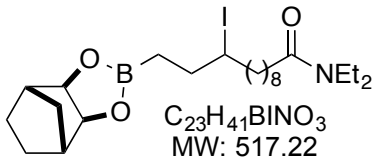


From undec-10-en-1-ol (0.21 mL, 1.0 mmol) following **GP2**. The crude residue was submitted to FCC purification (grad = 5-10-15-20% EtOAc/heptanes) to afford **4g** as a clear oil (331 mg, 0.739 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (br d, *J* = 1.4 Hz, 2H), 4.14 (tt, *J* = 8.7, 4.6

Hz, 1H), 3.64 (app t, J = 6.6 Hz, 2H), 2.26 (m, 2H), 1.97 – 1.77 (m, 3H), 1.76 – 1.62 (m, 1H), 1.60 – 1.45 (m, 5H), 1.39 – 1.23 (m, 12H), 1.19 (app dt, J = 11.1, 1.5 Hz, 1H), 1.03 (m, 2H), 0.95 (dd, J = 10.2, 6.2 Hz, 1H), 0.91 – 0.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.7, 63.1, 43.7, 40.9, 40.3, 35.2, 32.8, 30.7, 29.50, 29.46, 29.37 (two superimposed CH_2 peaks), 28.8, 25.7, 23.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.7 (s). IR (neat): 3352, 2924, 2853, 1456, 1387, 1371, 1321, 1283, 1224, 1169, 1132, 1027 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{35}O_3BI$ $[M+H]^+$: 449.1718; found: 449.1703.

6.2 Synthesis of 4l

***exo*-*N*,*N*-Diethyl-12-(hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)-10-iododododecanamide (4l)**

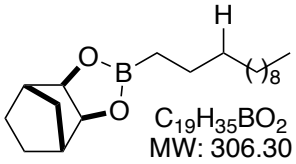


From **1l** (48 mg, 0.2 mmol) following **GP3** (NMR yield). A sample was submitted to FCC purification (20% EtOAc/heptanes) to perform the characterizations of **4l**, and **4l** was obtained as a pale orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, J = 1.1 Hz, 2H), 4.11 (tt, J = 8.6, 4.7 Hz, 1H), 3.31 (dq, J = 20.0, 7.1 Hz, 4H), 2.31 – 2.20 (m, 4H), 1.96 – 1.74 (m, 3H), 1.73 – 1.56 (m, 3H), 1.55 – 1.41 (m, 4H), 1.41 – 1.21 (m, 9H), 1.20 – 0.97 (m, 10H), 0.89 (ddd, J = 16.3, 10.2, 6.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 83.81, 83.80, 43.9, 40.9, 40.4, 35.3, 33.2, 30.8, 29.6, 29.54, 29.48, 29.4, 28.9, 25.6, 23.41, 23.40. ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9. IR (neat): 2927, 1641, 1371, 1223, 1028 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{42}O_3NBI$ $[M+H]^+$: 518.2297; found: 518.2286.

7. Experimental procedures and characterizations for the synthesis of alkyl norbornanediol boronic esters

7.1 Synthesis of 3a

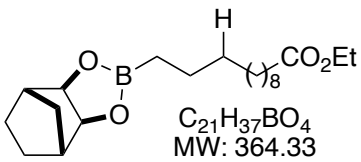
***exo*-2-Dodecylhexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborole (3a)**



A one-neck, 10 mL round-bottom flask was charged with **2a** (168 mg, 0.4 mmol, 1.0 equiv), H_3PO_2 (0.44 mL, 4.0 mmol, 10.0 equiv, 50 w% in water), Et_3N (0.6 mL, 4.4 mmol, 11.0 equiv, distilled prior to use) and AIBN (13 mg, 0.08 mmol, 20 mol%) in sequence the contents were heated at 90 °C for 1.5 h. Another portion of AIBN (13 mg, 0.08 mmol, 20 mol%) was added and the contents heated at 90 °C for a further 1.5 h. The contents were cooled to rt, partitioned between TBME (10 mL) and H_2O (10 mL) and shaken with sat. aq. $Na_2S_2O_3$ (10 mL). The ethereal phase was washed with water (10 mL), and the combined aqueous phases were back-extracted with TBME (5 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$ (10 mL), dried with sat. aq. NaCl (10 mL), then dried over Na_2SO_4, filtered over a short path of silica, and concentrated *in vacuo*. The crude residue was submitted to FCC purification (2% EtOAc/heptanes) to afford **3a** as a clear oil (108 mg, 0.35 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.19 (app br d, J = 1.3 Hz, 2H), 2.26 (br dq, J = 3.2, 1.6 Hz, 2H), 1.55 – 1.44 (m, 3H), 1.44 – 1.33 (m, 2H), 1.33 – 1.21 (m, 18H), 1.18 (app ddt, J = 10.8, 2.8, 1.4 Hz, 1H), 1.08 – 0.99 (m, 2H), 0.88 (app t, J = 7.0 Hz, 3H), 0.80 (dd, J_1 = J_2 = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.6, 40.9, 32.5, 31.9, 30.7, 29.70, 29.67, 29.58, 29.44, 29.37, 24.1, 23.4, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.2. IR (neat): 2995, 2922, 2874, 2852, 1408, 1383, 1372, 1321, 1220, 1031 cm^{-1}. Thermal Elemental Analysis calcd. for $C_{19}H_{35}BO_2$: C, 74.51; H, 11.52, N, 0.00; found: C, 75.06; H, 11.48, N, 0.00.

7.2 Synthesis of 3b and 3d following GP3

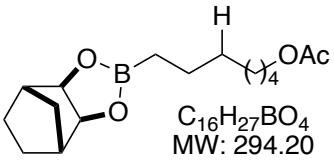
Ethyl *exo*-12-(hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)dodecanoate (3b)



From ethyl undec-10-enoate (0.29 mL, 2.0 mmol) following **GP4**. The crude residue was submitted to FCC purification (grad = 1-3-5-7% EtOAc/heptanes) to afford **3b** as a clear oil (446 mg, 1.23 mmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (app br d, J = 1.3 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.28 (app dd, J_1 = J_2 = 7.4 Hz, 2H), 2.29 – 2.23 (m, 2H), 1.67 – 1.53 (m, 3H), 1.53 – 1.45 (m, 2H), 1.45 – 1.34 (m, 2H), 1.34 – 1.22 (m, 17H), 1.17 (app dq, J = 10.8, 1.5 Hz, 1H), 1.05 (app td, J = 7.8, 7.2, 2.5 Hz, 2H), 0.80 (app dd, J_1 = J_2 = Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 83.6, 60.1, 40.9, 34.4, 32.5, 30.7, 29.6, 29.53, 29.47, 29.4, 29.3, 29.2, 25.0, 24.1, 23.4, 14.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.1. IR (neat):

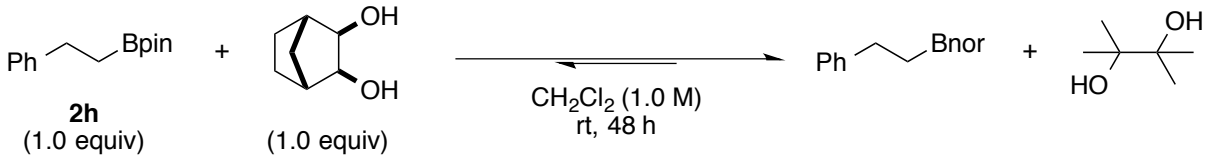
1734 (s) cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{21}H_{38}O_4B$ $[M+H]^+$: 365.2858; found: 365.2859.

***exo*-7-(Hexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)heptyl acetate (3d)**

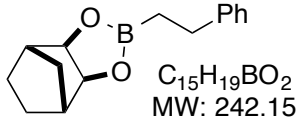


From 5-hexenyl acetate (0.33 mL, 2.0 mmol) following **GP4**. The crude residue was submitted to FCC purification (grad = 2-3-5-7-7% EtOAc/heptanes) to afford **3d** as a clear oil (452 mg, 1.54 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (app br d, J = 1.3 Hz, 2H), 4.04 (t, J = 6.7 Hz, 2H), 2.26 (app br dq, J = 3.3, 1.6 Hz, 2H), 2.04 (s, 3H), 1.67 – 1.53 (m, 3H), 1.52 – 1.45 (m, 2H), 1.44 – 1.35 (m, 2H), 1.35 – 1.26 (m, 6H), 1.18 (app dt, J = 10.9, 1.4 Hz, 1H), 1.08 – 0.99 (m, 2H), 0.80 (dd, $J_1 = J_2$ = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 83.6, 64.7, 40.9, 32.3, 30.7, 29.0, 28.6, 25.8, 24.0, 23.4, 21.0. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.3. IR (neat): 1737 (s) cm^{-1}. Only the characteristic acyclic, saturated ester carbonyl stretch is reported. HRMS (ESI) calcd. for $C_{16}H_{28}O_4B$ $[M+H]^+$: 295.2075; found: 295.2071.

7.3 Synthesis of 3h by boron-transesterification



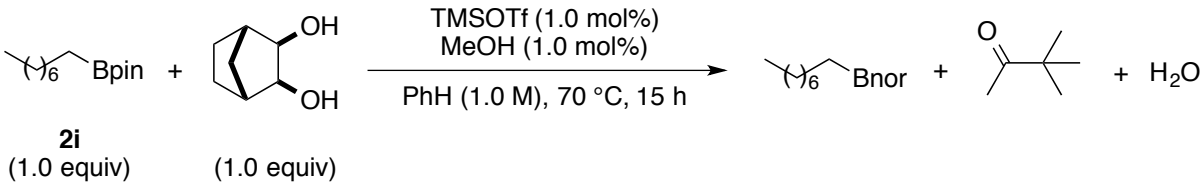
***exo*-2-Phenethylhexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol (3h)**



To a one-neck, 25 mL round-bottom flask were added **2h** (1.0 equiv), **SI-1** (641 mg, 5.0 mmol, 1.0 equiv) and CH_2Cl_2 (5 mL, 1.0 M) and the contents were left to stir at rt for 48 h. The reaction mixture was then concentrated *in vacuo* and the resulting residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **3h**[§] as a clear oil (1.16 g, 4.8 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.05 (m, 5H), 4.11 (d, J = 1.0 Hz, 2H), 2.67 (app dd, J = 8.1 Hz, 2H), 2.17 (dq, J = 3.4, 1.7 Hz, 2H), 1.44 – 1.30 (m, 3H), 1.14 – 1.01 (m, 3H), 0.99 – 0.87 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 128.3, 128.0, 125.6, 83.8, 40.9, 30.7, 30.1, 23.4. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.1. IR (neat): 2954, 2875, 1371, 1321, 1220, 1166,

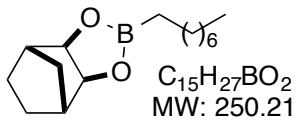
1030, 749, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{19}O_2BNa$ $[M+Na]^+$: 265.1370; found: 265.1369. [§]Contaminated with 7 mol% of **2h**.

7.4 Synthesis of 3i by acid catalyzed boron-transesterification



2i (1.0 equiv) (1.0 equiv)

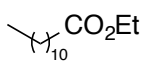
***exo*-2-Octylhexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborole (3i)**



To a one-neck, 50 mL round-bottom flask were added **2i** (1.78 g, 7.4 mmol, 1.0 equiv), **SI-1** (948 mg, 7.4 mmol, 1.0 equiv), PhH (7.4 mL, 1.0 M), TMSOTf (1.48 mL, 0.074 mmol, 1.0 mol%, 0.05 M in CH_2Cl_2) and MeOH (3 µL, 0.074 mmol, 1.0 mol%) in sequence and the contents were stirred at 70 °C for 15 h. The contents were cooled to rt, partitioned between TBME (10 mL) and H_2O (10 mL) and shaken with sat. aq. $NaHCO_3$ (10 mL). The ethereal phase was washed with water (10 mL), and the combined aqueous phases were back-extracted with TBME (5 mL). The combined ethereal phases were dried with sat. aq. NaCl (10 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (DCM 100%) to afford **3i** as a clear oil (1.78 g, 7.1 mmol, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, J = 1.0 Hz, 2H), 2.25 (dq, J = 3.4, 1.7 Hz, 2H), 1.57 – 1.44 (m, 3H), 1.43 – 1.33 (m, 2H), 1.31 – 1.22 (m, 10H), 1.16 (dp, J = 10.9, 1.4 Hz, 1H), 1.07 – 0.97 (m, 2H), 0.86 (app t, J = 7.0 Hz, 3H), 0.82 – 0.73 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.7, 41.0, 32.6, 32.0, 30.8, 29.5, 29.4, 24.2, 23.5, 22.8, 14.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.3. IR (neat): 2923, 2854, 1372, 1322, 1222, 1030 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{26}O_2B$ $[M-H]^+$: 249.2020; found: 249.2017.

8. Experimental Procedures and Characterizations for the Synthesis of Methylated Alkenes

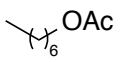
Ethyl laurate (5b)



$C_{14}H_{28}O_2$
MW: 228.21

From ethyl 10-undecenoate (200 μL, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (9:1 pentane/CH_2Cl_2) to afford **5b** as a light-yellow oil (83 mg, 0.48 mmol, 48%). Spectral data compared with a commercially available sample [CAS Number: 106-33-2]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 2.26 (app t, *J* = 7.5 Hz, 2H), 1.59 (app p, *J* = 7.2 Hz, 2H), 1.30 – 1.20 (m, 19H), 0.85 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 60.2, 34.5, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.4, 14.2.

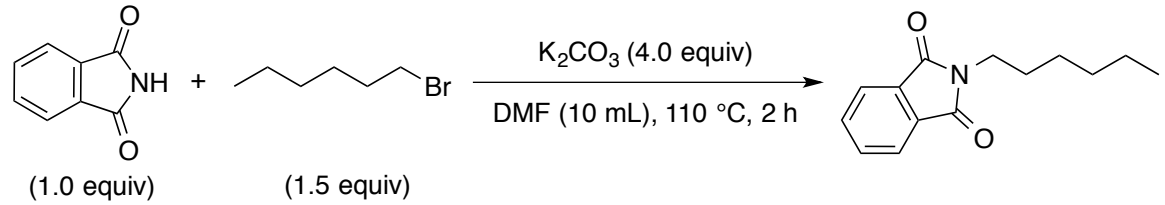
Heptyl acetate (5d)

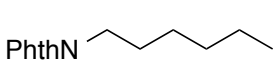


$C_9H_{18}O_2$
MW: 158.13

From 5-hexenyl acetate (165 μL, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (99:1 to 9:1 heptanes/EtOAc) to afford **5d** as a colorless liquid (122 mg, 0.77 mmol, 77%). Spectral data compared with a commercially available sample [CAS Number: 112-06-1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (t, *J* = 6.8 Hz, 2H), 1.98 (s, 3H), 1.56 (app p, *J* = 6.9 Hz, 2H), 1.31 – 1.23 (m, 8H), 0.83 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 64.6, 31.8, 29.0, 28.7, 25.9, 22.6, 21.0, 14.0.

2-Hexylisoindoline-1,3-dione (5j)



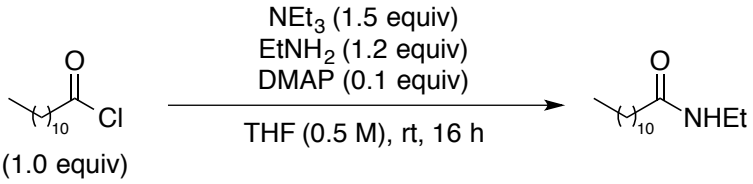


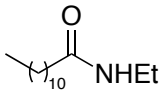
$C_{14}H_{17}NO_2$
MW: 231.13

A one-neck, 50 mL round-bottom flask was charged with phthalimide (1.62 g, 11.0 mmol, 1.0 equiv), hexyl bromide (2.64 g, 16.0 mmol, 1.5 equiv) and potassium carbonate (6.08 g, 44.0 mmol, 4.0 equiv). The contents were dissolved in DMF (10 mL, 1.1 M) and the resulting mixture was heated up to 120 °C and stirred open to air for 2 h. The contents were then cooled to rt and partitioned between H_2O (100 mL) and Et_2O (100 mL). The ethereal phase was washed with H_2O (3×100 mL), dried with sat. aq. NaCl (100 mL), then dried with Na_2SO_4, filtered, and evaporated *in vacuo* to afford **5j** as colorless crystals (2.42 g, 10.5 mmol, 95%). Spectral and physical data were in accordance with the literature.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.72 – 7.66 (m, 2H), 3.67 (dd, *J* = 7.9, 6.7 Hz, 2H), 1.71 – 1.61 (m, 2H), 1.38 –

1.25 (m, 6H), 0.90 – 0.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 134.0, 132.3, 123.3, 38.2, 31.5, 28.9, 26.7, 22.6, 14.1.

_N_-Ethyldodecanamide (5k)

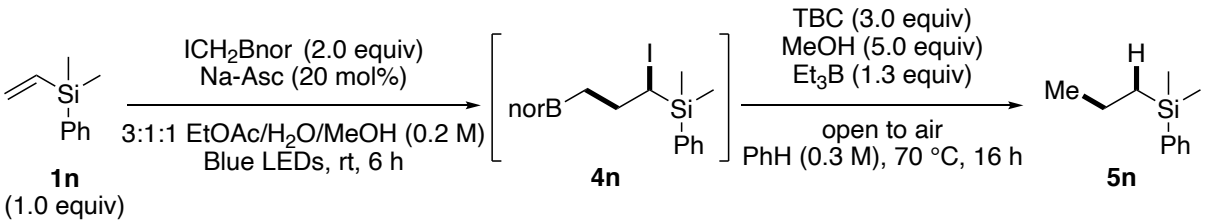


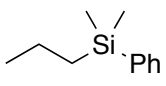


$C_{14}H_{29}NO$
MW: 227.23

A one-neck, 100 mL round-bottom flask was charged with triethylamine (2.1 mL, 15.0 mmol, 1.5 equiv), 4-dimethylaminopyridine, DMAP (120 mg, 1.0 mmol, 0.1 equiv), ethylamine (0.79 mL, 120.0 mmol, 12.0 equiv, 2.0 M in THF) and THF (20 mL, 0.5 M). The contents were cooled to 0 °C and lauroyl chloride (2.31 mL, 10.0 mmol, 1.0 equiv) was added dropwise. The reaction mixture was then stirred at rt for 16 h. The contents were partitioned between TBME (40 mL) and 2.0 M aq. HCl (40 mL) and the resulting solution was stirred for 30 min at rt. The two phases were separated and the ethereal phase was washed with 2.0 M aq. HCl (40 mL), then 1.0 M aq. NaOH (40 mL), sat. aq. $NaHCO_3$ (40 mL), sat. aq. NaCl (40 mL), dried over Na_2SO_4, filtered through a silica plug and the volatiles were removed *in vacuo* to afford **5k** as white crystals (1.56 g, 6.9 mmol, 69%). Spectral and physical data were in accordance with the literature.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (bs, 1H), 3.26 (q, *J* = 7.2 Hz, 1H, overlapping), 3.24 (q, *J* = 7.2 Hz, 1H, overlapping), 2.12 (dd, *J* = 8.5, 6.7 Hz, 2H), 1.59 (app p, *J* = 7.3 Hz, 2H), 1.29 – 1.23 (m, 16H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.85 (app t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 37.0, 34.4, 32.0, 29.7, 29.6, 29.5, 29.4, 25.9, 22.8, 15.0, 14.2.

Dimethyl(phenyl)(propyl)silane (5n)



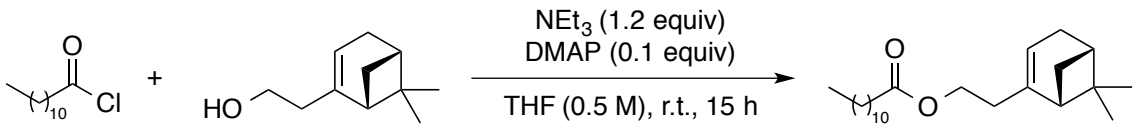


$C_{11}H_{18}Si$
MW: 178.12

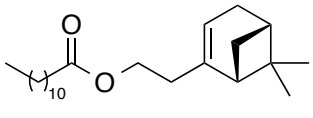
A one-neck, 25 mL round-bottom flask was charged with **ICH$_2$Bnor** (2540 mg, 2.0 mmol, 2.0 equiv), sodium ascorbate, Na-Asc (40 mg, 0.02 mmol, 20 mol%), **1n** (182 µL, 1.0 mmol, 1.0 equiv), EtOAc (3 mL), H_2O (1 mL) and MeOH (1 mL). The resulting mixture was degassed for about 5 min under a gentle flux of N_2 atm and the flask was closed with a glass stopper. The contents were

vigorously stirred under Blue LEDs irradiation (390 nm) for 6 h, with fan-cooling. The contents were then partitioned between sat. aq. $Na_2S_2O_3$ and TBME. The aqueous phase was back-extracted twice. The combined ethereal phase was washed with sat. aq. $NaHCO_3$, dried with sat. aq. NaCl, then dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dissolved in PhH (0.3 M), and transferred to a one-neck, round bottom flask equipped with a condenser. *tert*-Butyl catechol, TBC (3.0 equiv), MeOH (5.0 equiv) and triethylborane, Et_3B (2 M in PhH, 1.3 equiv) were added in sequence and the resulting mixture was heated at 70 °C for 16 h, open to air. The contents were cooled to rt, partitioned between TBME (10 mL) and H_2O (10 mL) and shaken with sat. aq. $Na_2S_2O_3$ (5 mL). The ethereal phase was washed with water (10 mL), and the combined aqueous phases were back-extracted with TBME (5 mL). The combined ethereal phase was washed with sat. aq. $NaHCO_3$ (15 mL), dried with sat. aq. NaCl (15 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (pentane) to afford **5n** as a colorless oil (80 mg, 0.45 mmol, 45%). Spectral and physical data were in accordance with the literature.[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 2H), 7.41 – 7.33 (m, 3H), 1.47 – 1.27 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.83 – 0.71 (m, 2H), 0.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 133.7, 128.9, 127.8, 18.54, 18.45, 17.6, -2.8.

2-((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl dodecanoate (5p)



1.2 equiv 1.0 equiv

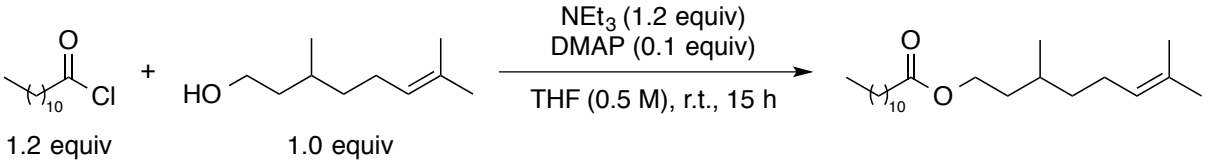


$C_{23}H_{40}O_2$
MW: 348.30

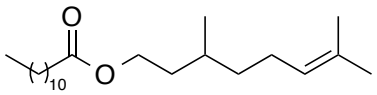
A one-neck, 100 mL round-bottom flask was charged with (–)-Nopol (2.00 mL, 11.4 mmol, 1.0 equiv), DMAP (125 mg, 1.0 mmol, 0.09 equiv), THF (25 mL, 0.5 M) and Et_3N (1.9 mL, 13.6 mmol, 1.2 equiv) and the contents were cooled to 0 °C. Lauroyl chloride (2.8 mL, 13.6 mmol, 1.2 equiv) was added dropwise at this temperature, and then the reaction mixture was warmed up to r.t. and stirred for 15 h. The contents were partitioned between TBME (20 mL) and 2.0 M aq. HCl (20 mL) and the resulting solution was stirred at rt for 10 min. The two phases were separated and the ethereal phase was washed with 2.0 M aq. HCl (20 mL). The combined aqueous phases were back-extracted with TBME (10 mL). The combined ethereal phases were then washed with sat. aq. $NaHCO_3$ (40 mL), sat. aq. NaCl (40 mL), dried over Na_2SO_4, filtered through a silica plug and concentrated

in vacuo. The crude residue was purified by FCC on silica gel (2% EtOAc in heptanes) to afford **5p** as a colorless oil (3.47 g, 10.0 mmol, 87%). $[\alpha]_D^{20}$ – 21.0º (*c* 1.00, $CHCl_3$ (HPLC grade, stabilized on EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (tp, *J* = 2.8, 1.4 Hz, 1H), 4.07 (td, *J* = 7.0, 2.8 Hz, 2H), 2.36 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.31 – 2.19 (m, 6H), 2.11 – 2.02 (m, 2H), 1.60 (app p, *J* = 7.3 Hz, 2H), 1.34 – 1.22 (m, 19H), 1.14 (d, *J* = 8.5 Hz, 1H), 0.88 (app t, *J* = 6.8 Hz, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 144.4, 118.9, 62.6, 45.8, 40.9, 38.1, 36.1, 34.6, 32.1, 31.8, 31.5, 29.8, 29.6, 29.5, 29.4, 29.3, 26.4, 25.1, 22.8, 21.3, 14.3. IR (neat): 2921, 2853, 1738, 1466, 1160 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{41}O_2$ $[M+H]^+$: 349.3101; found: 349.3103.

3,7-Dimethyloct-6-en-1-yl dodecanoate (5q)



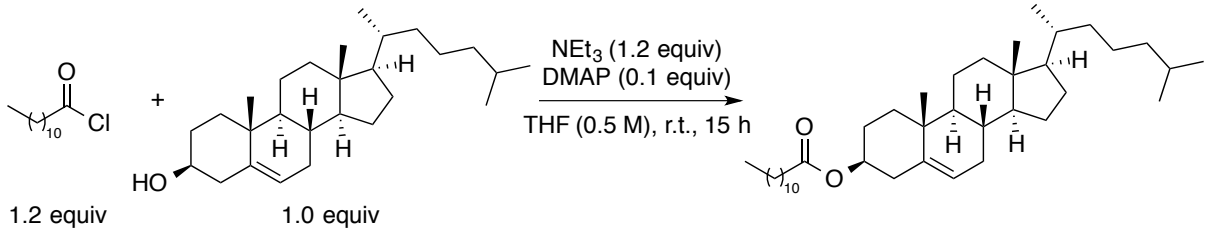
1.2 equiv 1.0 equiv

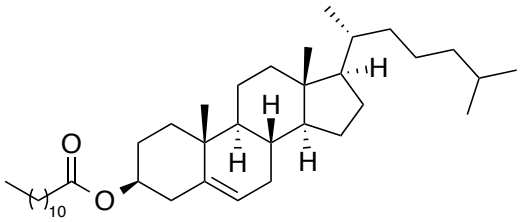


$C_{22}H_{42}O_2$
MW: 338.32

A one-neck, round-bottom flask was charged with β-Citronellol (2.00 mL, 11.1 mmol, 1.0 equiv), DMAP (125 mg, 1.0 mmol, 0.09 equiv), THF (25 mL, 0.5 M) and Et_3N (1.8 mL, 12.0 mmol, 1.1 equiv) and the contents were cooled to 0 °C. Lauroyl chloride (2.8 mL, 13.3 mmol, 1.2 equiv) was added dropwise at this temperature, and then the reaction mixture was warmed up to r.t. and stirred for 15 h. The contents were partitioned between TBME (20 mL) and 2.0 M aq. HCl (20 mL) and the resulting solution was stirred for 10 min at r.t. The two phases were separated and the ethereal phase was washed with 2.0 M aq. HCl (20 mL). The combined aqueous phases were back-extracted with TBME (10 mL). The combined ethereal phases were then washed with sat. aq. $NaHCO_3$ (40 mL), sat. aq. NaCl (40 mL), dried over Na_2SO_4, filtered through a silica plug and the volatiles were removed *in vacuo*. The crude residue was purified by FCC on silica gel (2% EtOAc in heptanes) to afford **5q** as a colorless oil (3.64 g, 10.8 mmol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (tp, *J* = 5.8, 1.5 Hz, 1H), 4.09 (ddt, *J* = 10.9, 7.3, 3.4 Hz, 2H), 2.28 (app t, *J* = 7.5 Hz, 2H), 1.98 (p, *J* = 7.4 Hz, 2H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.63 – 1.51 (m, 6H), 1.49 – 1.41 (m, 1H), 1.39 – 1.12 (m, 19H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.88 (app t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 131.5, 124.7, 62.9, 37.1, 35.6, 34.6, 32.1, 29.8, 29.64, 29.62, 29.5, 29.4, 29.3, 25.9, 25.5, 25.2, 22.8, 19.6, 17.8, 14.3. IR (neat): 2922, 2853, 1738, 1456, 1169 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{43}O_2$ $[M+H]^+$: 339.3258; found: 339.3254.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10, 11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yldodecanoate (5r)





$C_{39}H_{68}O_2$
MW: 568.52

A one-neck, round-bottom flask was charged with Cholesterol (2.00 g, 10.0 mmol, 1.0 equiv), DMAP (125 mg, 1.0 mmol, 0.1 equiv), THF (25 mL, 0.5 M) and Et_3N (1.8 mL, 12.0 mmol, 1.2 equiv) and the contents were cooled to 0 °C. Lauroyl chloride (2.5 mL, 12.0 mmol, 1.2 equiv) was added dropwise at this temperature, and then the reaction mixture was warmed up to rt and stirred for 15 h. The contents were partitioned between TBME (20 mL) and 2.0 M aq. HCl (20 mL) and the resulting solution was stirred for 10 min at rt. The two phases were separated and the ethereal phase was washed with 2.0 M aq. HCl (20 mL). The combined aqueous phases were back-extracted with TBME (10 mL). The combined ethereal phases were then washed with sat. aq. $NaHCO_3$ (40 mL), sat. aq. NaCl (40 mL), dried over Na_2SO_4, filtered through a silica plug and the volatiles were removed *in vacuo*. The crude residue was crystallized from EtOH to give **5r** as white-translucent crystals (2.2 g, 3.9 mmol, 39%). m.p. = 89.9 – 90.4 °C (EtOH). $[\alpha]_D^{20}$ – 27.7º (*c* 1.00, $CHCl_3$ (HPLC grade, stabilized on EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (app d, *J* = 4.2 Hz, 1H), 4.66 – 4.56 (m, 1H), 2.32 – 2.24 (m, 4H), 2.03 –1.94 (m, 2H), 1.87 – 1.80 (m, 3H), 1.68 – 1.42 (m, 10H), 1.35 – 1.26 (m, 20H), 1.17 – 1.07 (m, 6H), 1.04 – 0.96 (m, 6H [containing 1.02 (s, 3H)]), 0.94 – 0.89 (m, 4H [containing 0.91 (d, *J* = 6.6 Hz, 3H)]), 0.88 – 0.84 (m, 8H [containing 0.87 (d, *J* = 6.9 Hz, 3H) and 0.86 (s, *J* = 6.6 Hz, 3H)]), 0.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 139.9, 122.7, 73.8, 56.8, 56.3, 50.2, 42.5, 39.9, 39.7, 38.3, 37.2, 36.8, 36.3, 36.0, 34.9, 32.1, 32.0, 29.8, 29.6, 29.5, 29.4, 29.3, 28.4, 28.2, 28.0, 25.2, 24.4, 24.0, 23.0, 22.8, 22.7, 21.2, 19.5, 18.9, 14.3, 12.0. IR (neat): 2924, 2850, 1733, 1467, 1168, 723 cm^{-1}. HRMS (ESI) calcd. for $C_{39}H_{69}O_2$ $[M+H]^+$: 569.5292; found: 569.5285.

9. GC chromatograms

9.1 Chromatograms for the GC yields using GP5

Dodecane (5a)

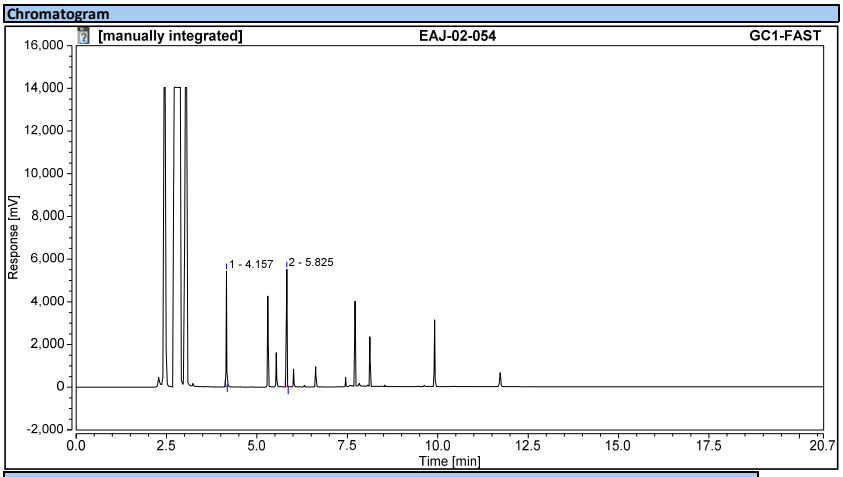
From 1-undecene (85 µL, 0.4 mmol) following **GP5**, to afford **5a** (RT = 5.825 min) in 60% GC yield (internal standard: nonane, RT = 4.157 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-02-054**	*Run Time (min):*	**20.67**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**25/Nov/19 09:33**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		4.157	99.613	5411.327	52.73	49.59
2		5.825	89.283	5501.342	47.27	50.41
Total:			**188.896**	**10912.669**	**100.00**	**100.00**

Ethyl laurate (5b)

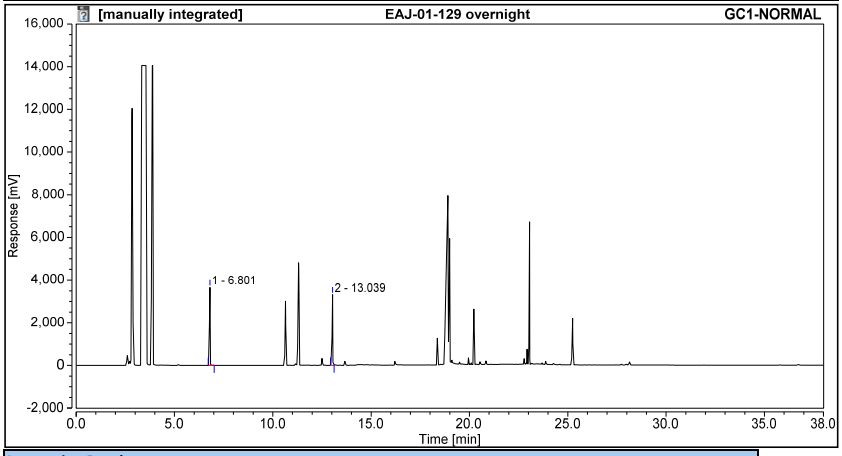
From ethyl undec-10-enoate (62 mg, 0.4 mmol) following **GP5**, to afford **5b** (RT = 13.039 min) in 74% GC yield (internal standard: nonane, RT = 6.801 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-129 overnight**	*Run Time (min):*	**38.00**
Vial Number:	**3**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**26/Jun/19 08:42**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		6.801	138.027	3651.660	51.47	52.46
2		13.039	130.132	3308.776	48.53	47.54
Total:			**268.159**	**6960.436**	**100.00**	**100.00**

Heptyl acetate (5d)

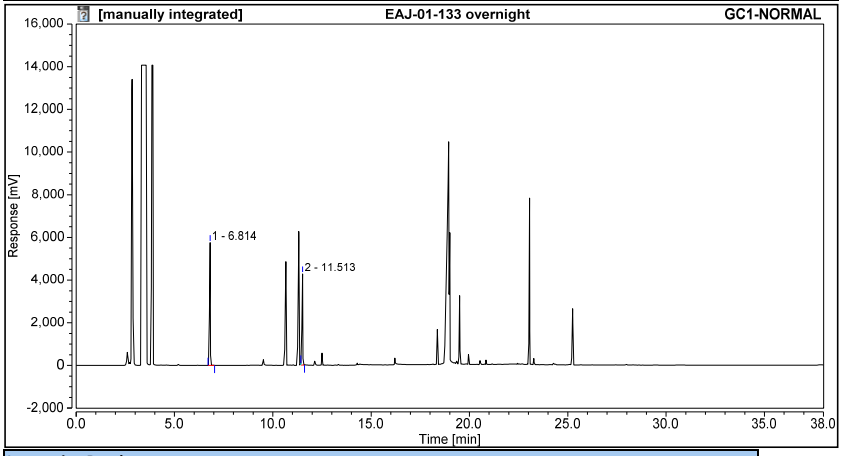
From 5-hexenyl acetate (66 µL, 0.4 mmol) following **GP5**, to afford **5d** (RT = 11.513 min) in 86% GC yield (internal standard: nonane, RT = 6.814 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-133 overnight**	*Run Time (min):*	**38.00**
Vial Number:	**4**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**03/Jul/19 14:36**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		6.814	250.372	5745.864	57.83	57.42
2		11.513	182.580	4261.531	42.17	42.58
Total:			**432.953**	**10007.395**	**100.00**	**100.00**

Pentylbenzene (5f)

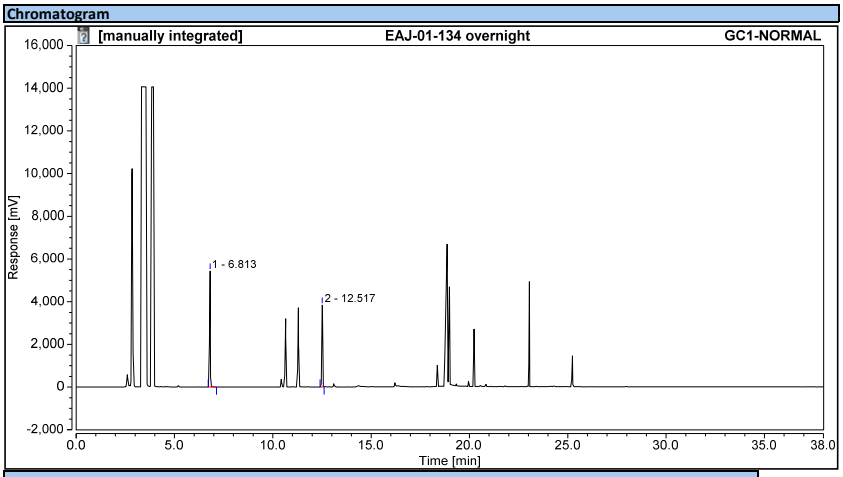
From 4-phenyl-1-butene (61 µL, 0.4 mmol) following **GP5**, to afford **5f** (RT = 12.517 min) in 45% GC yield (internal standard: nonane, RT = 6.813 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-134 overnight**	*Run Time (min):*	**38.00**
Vial Number:	**5**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**03/Jul/19 13:02**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		6.813	227.474	5429.368	59.51	58.62
2		12.517	154.745	3832.655	40.49	41.38
Total:			**382.219**	**9262.023**	**100.00**	**100.00**

2-Hexylisoindoline-1,3-dione (5j)

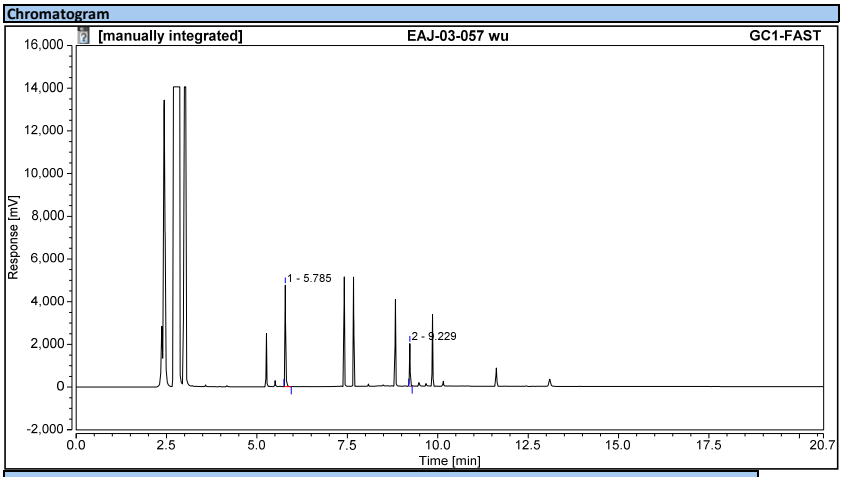
From 2-(pent-4-en-1-yl)isoindoline-1,3-dione (108 mg, 0.5 mmol) following **GP5**, to afford **5j** (RT = 9.229 min) in 24% GC yield (internal standard: dodecane, RT = 5.785 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-057 wu**	*Run Time (min):*	**20.67**
Vial Number:	**6**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**01/Jul/20 07:18**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.785	97.838	4751.918	70.88	70.40
2		9.229	40.197	1997.787	29.12	29.60
Total:			**138.035**	**6749.705**	**100.00**	**100.00**

N-Ethyldodecanamide (5k)

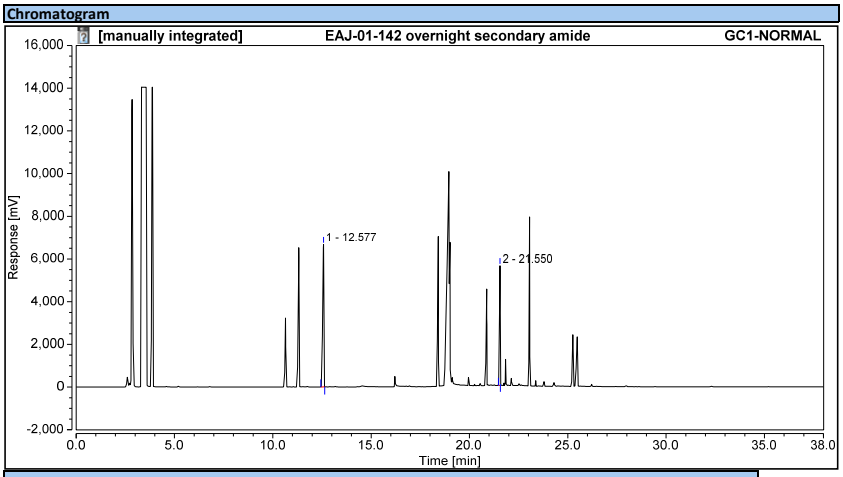
From *N*-ethylundec-10-enamide[4] (85 mg, 0.4 mmol) following **GP5**, to afford **5k** (RT = 21.550 min) in 47% GC yield (internal standard: dodecane, RT = 12.577 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-142 overnight secondary amide**	*Run Time (min):*	**38.00**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**05/Jul/19 11:14**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		12.577	379.873	6666.948	63.81	54.34
2		21.550	215.408	5601.439	36.19	45.66
Total:			**595.281**	**12268.386**	**100.00**	**100.00**

N,N-Diethyldodecanamide (5l)

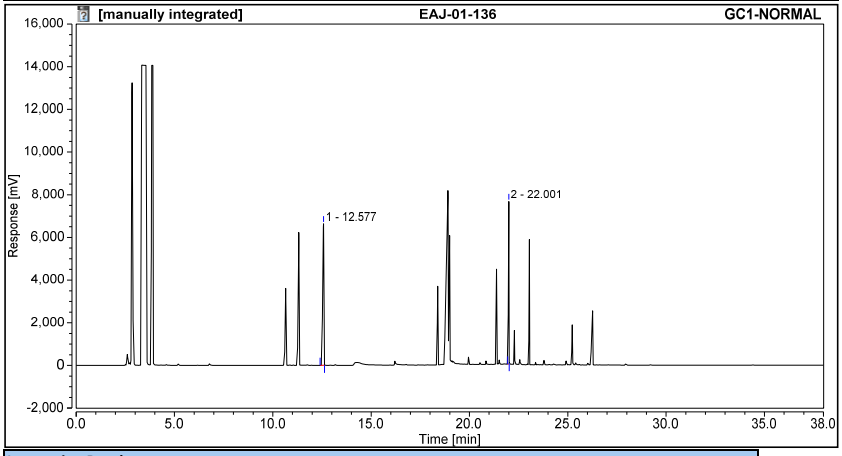
From *N,N*-diethylundec-10-enamide[4] (96 mg, 0.4 mmol) following **GP5**, to afford **5l** (RT = 22.001 min) in 65% GC yield (internal standard: dodecane, RT = 12.577 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-136**	*Run Time (min):*	**38.00**
Vial Number:	**6**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**03/Jul/19 13:49**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		12.577	371.929	6630.830	63.47	46.54
2		22.001	214.035	7618.134	36.53	53.46
Total:			**585.964**	**14248.964**	**100.00**	**100.00**

1-Bromododecane (5m)

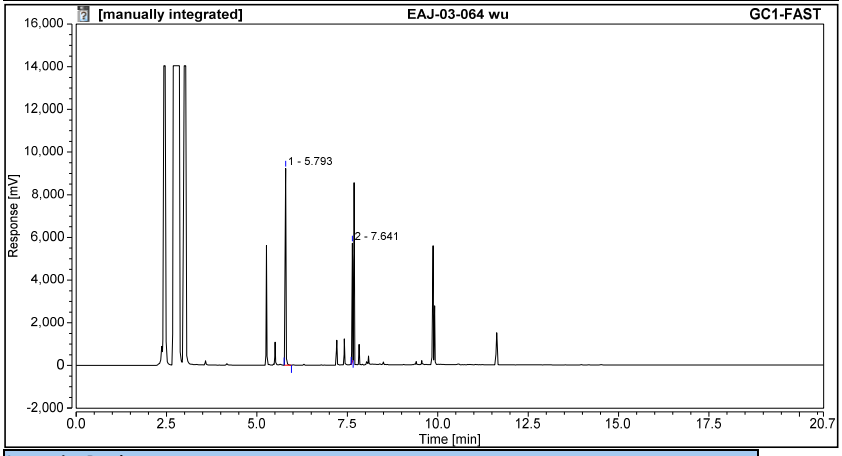
From 11-bromo-1-undecene (110 µL, 0.5 mmol) following **GP5**, to afford **5m** (RT = 7.641 min) in 21% GC yield (internal standard: dodecane, RT = 5.793 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-064 wu**	*Run Time (min):*	**20.67**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**07/Jul/20 15:22**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.793	180.124	9220.861	59.92	62.42
2		7.641	120.464	5551.666	40.08	37.58
Total:			**300.588**	**14772.528**	**100.00**	**100.00**

Dimethyl(phenyl)(propyl)silane (5n)

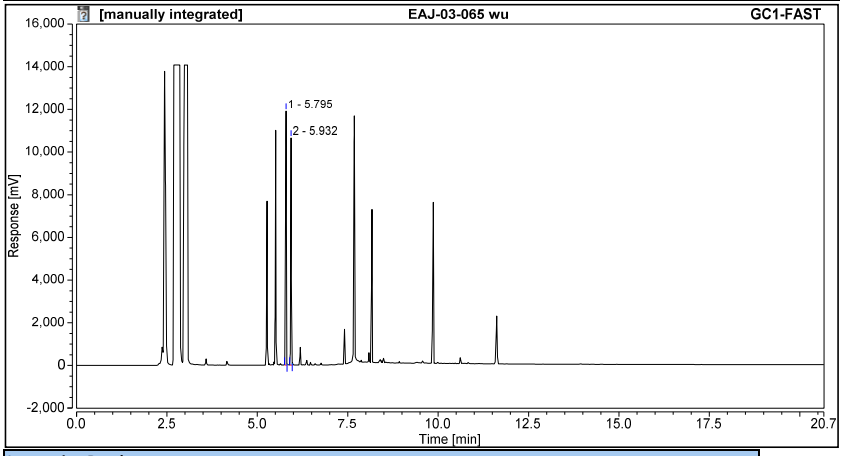
From dimethylphenylvinylsilane (91 μL, 0.5 mmol) following **GP5**, to afford **5n** (RT = 5.932 min) in 41% GC yield (internal standard: dodecane, RT = 5.795 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-065 wu**	*Run Time (min):*	**20.67**
Vial Number:	**2**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**07/Jul/20 15:52**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.795	262.614	11898.184	56.74	52.79
2		5.932	200.226	10641.406	43.26	47.21
Total:			**462.840**	**22539.590**	**100.00**	**100.00**

1-(3,4-Methylenedioxyphenyl)butane (5o)

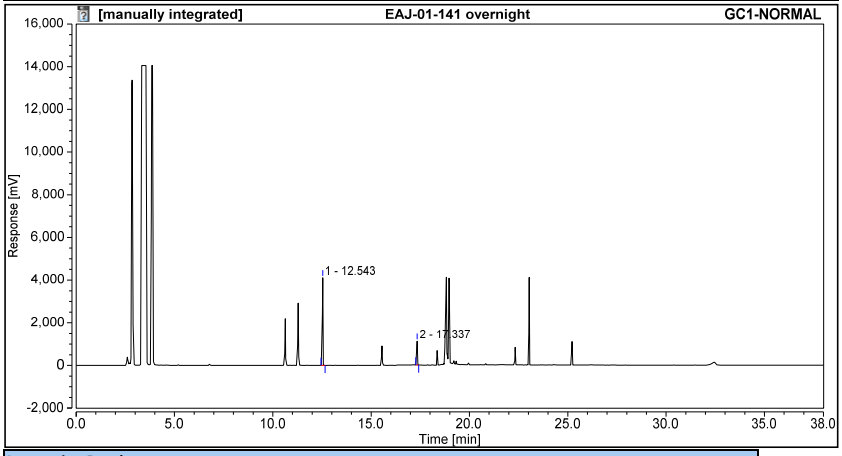
From safrole (59 µL, 0.4 mmol) following **GP5**, to afford **5o** (RT = 17.337 min) in 24% GC yield (internal standard: dodecane, RT = 12.543 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-141 overnight**	*Run Time (min):*	**38.00**
Vial Number:	**2**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**05/Jul/19 12:01**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		12.543	178.986	4104.536	82.33	78.60
2		17.337	38.427	1117.554	17.67	21.40
Total:			**217.413**	**5222.089**	**100.00**	**100.00**

2-((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl dodecanoate (5p)

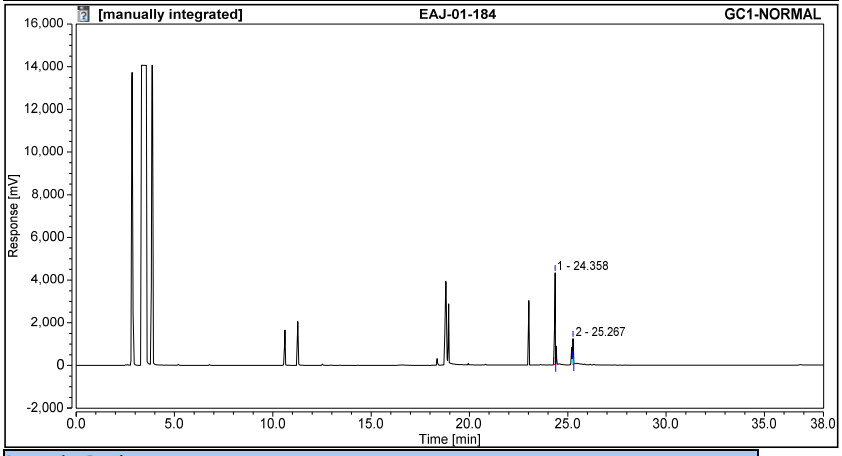
From (−)-nopyl undec-10-enoate[4] (133 mg, 0.4 mmol) following **GP5**, to afford **5p** (RT = 25.267 min) in 35% GC yield (internal standard: tetracosane, RT = 24.358 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-184**	*Run Time (min):*	**38.00**
Vial Number:	**7**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**18/Sep/19 09:32**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		24.358	165.370	4287.943	79.03	78.06
2		25.267	43.876	1205.424	20.97	21.94
Total:			**209.246**	**5493.367**	**100.00**	**100.00**

3,7-Dimethyloct-6-en-1-yl dodecanoate (5q)

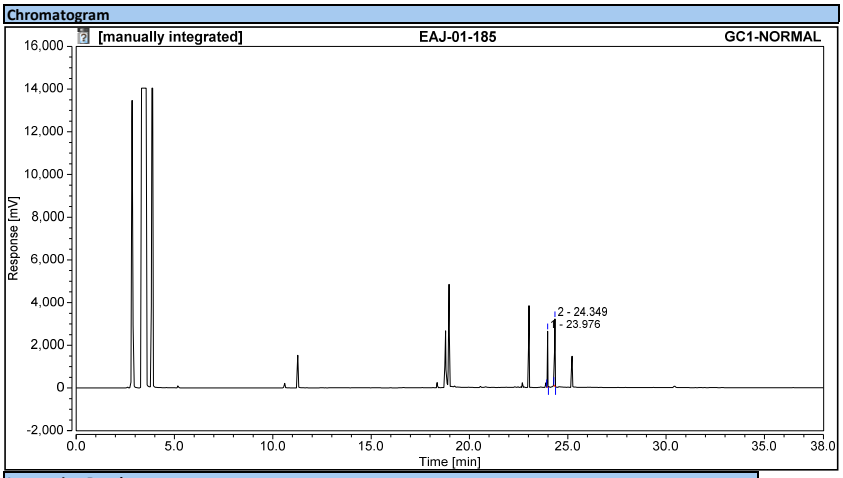
From β-citronellyl undec-10-enoate[4] (101 mg, 0.4 mmol) following **GP5**, to afford **5q** (RT = 24.349 min) in 10% GC yield (internal standard: nonadecane, RT = 23.976 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-01-185**	*Run Time (min):*	**38.00**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-NORMAL**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/Sep/19 08:41**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		23.976	74.348	2619.753	40.29	45.35
2		24.349	110.196	3156.940	59.71	54.65
Total:			**184.544**	**5776.693**	**100.00**	**100.00**

9.2 Chromatograms for the GC yields using GP6

Dodecane (5a)

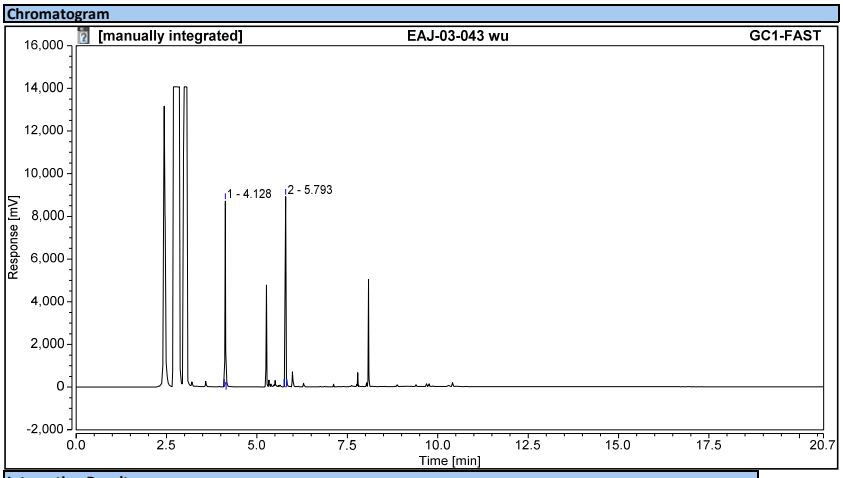
From 1-undecene (110 µL, 0.5 mmol) following **GP6**, to afford **5a** (RT = 5.793 min) in 48% GC yield (internal standard: nonane, RT = 4.128 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-043 wu**	*Run Time (min):*	**20.67**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/Jun/20 10:19**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		4.128	168.191	8562.506	50.39	49.02
2		5.793	165.593	8904.492	49.61	50.98
Total:			**333.784**	**17466.998**	**100.00**	**100.00**

Methyl laurate (5c)

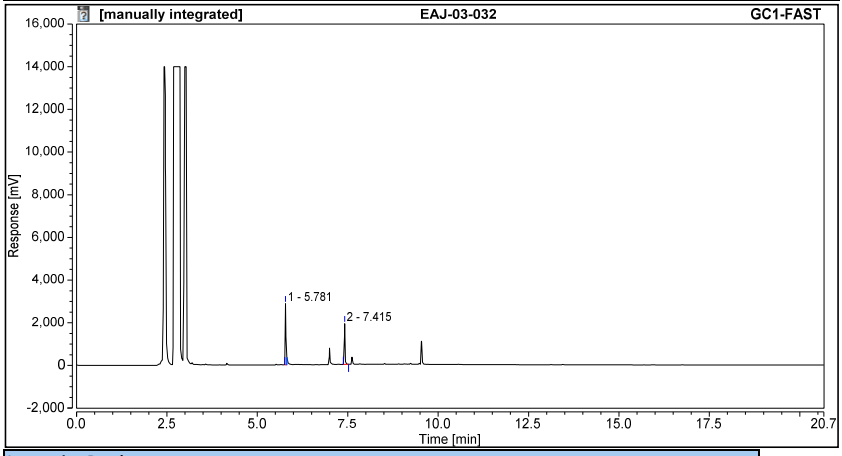
From methyl undec-10-enoate (99 mg, 0.5 mmol) following **GP6**, to afford **5c** (RT = 7.415 min) in 70% GC yield (internal standard: dodecane, RT = 5.781 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-032**	*Run Time (min):*	**20.67**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**18/Jun/20 08:27**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.781	58.749	2864.773	61.45	60.06
2		7.415	36.855	1905.357	38.55	39.94
Total:			**95.604**	**4770.129**	**100.00**	**100.00**

Heptyl acetate (5d)

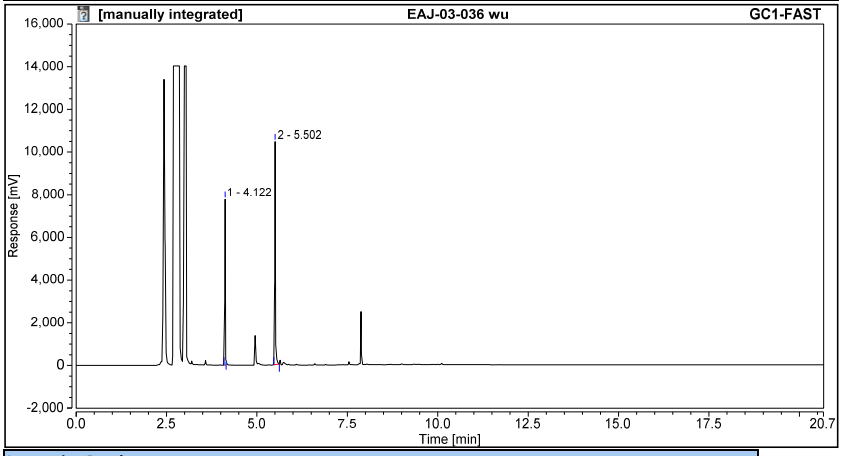
From 5-hexenyl acetate (83 µL, 0.5 mmol) following **GP6**, to afford **5d** (RT = 5.502 min) in 64% GC yield (internal standard: nonane, RT = 4.122 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-036 wu**	*Run Time (min):*	**20.67**
Vial Number:	**4**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**18/Jun/20 08:56**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		4.122	155.755	7774.078	39.90	42.66
2		5.502	234.604	10451.045	60.10	57.34
Total:			**390.359**	**18225.123**	**100.00**	**100.00**

Pentylbenzene (5f)

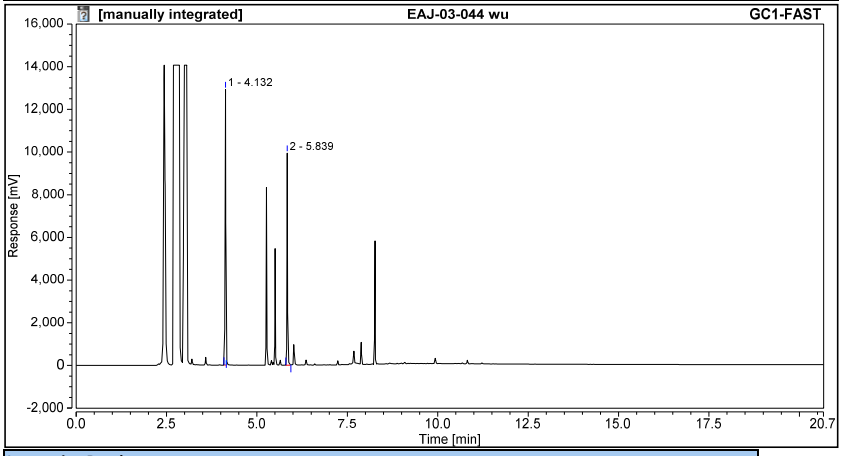
From 4-phenyl-1-butene (76 µL, 0.5 mmol) following **GP6**, to afford **5f** (RT = 5.839 min) in 39% GC yield (internal standard: nonane, RT = 4.132 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-044 wu**	*Run Time (min):*	**20.67**
Vial Number:	**2**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/Jun/20 10:48**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		4.132	284.591	12911.532	59.21	56.52
2		5.839	196.038	9931.553	40.79	43.48
Total:			**480.629**	**22843.085**	**100.00**	**100.00**

2-Hexylisoindoline-1,3-dione (5j)

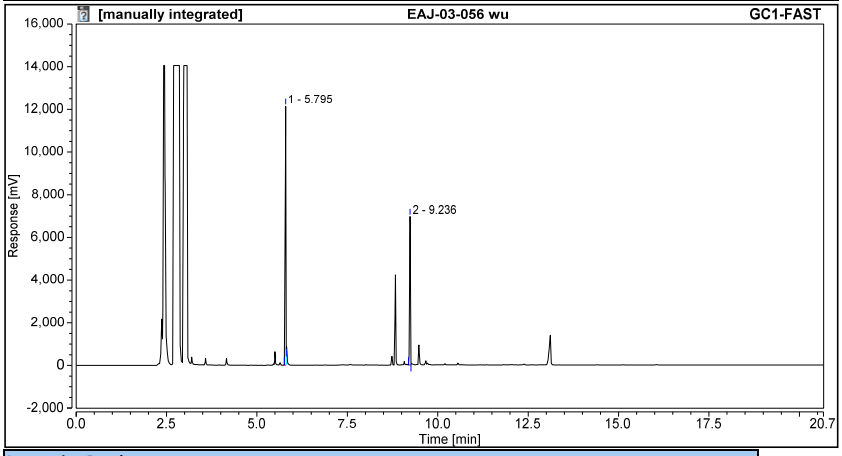
From 2-(pent-4-en-1-yl)isoindoline-1,3-dione (108 mg, 0.5 mmol) following **GP6**, to afford **5j** (RT = 9.236 min) in 33% GC yield (internal standard: dodecane, RT = 5.795 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-056 wu**	*Run Time (min):*	**20.67**
Vial Number:	**1**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**30/Jun/20 08:29**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.795	240.795	12127.167	60.84	63.56
2		9.236	154.992	6953.185	39.16	36.44
Total:			**395.787**	**19080.352**	**100.00**	**100.00**

N-Ethyldodecanamide (5k)

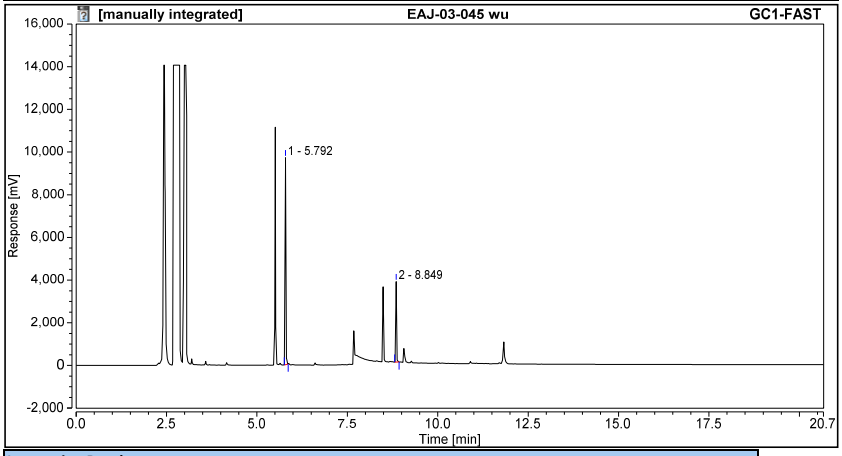
From *N*-ethylundec-10-enamide[4] (106 mg, 0.5 mmol) following **GP6**, to afford **5k** (RT = 8.849 min) in 18% GC yield (internal standard: dodecane, RT = 5.792 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-045 wu**	*Run Time (min):*	**20.67**
Vial Number:	**3**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/Jun/20 11:18**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.792	191.434	9694.993	71.48	72.02
2		8.849	76.394	3767.214	28.52	27.98
Total:			**267.828**	**13462.207**	**100.00**	**100.00**

N,N-Diethyldodecanamide (5l)

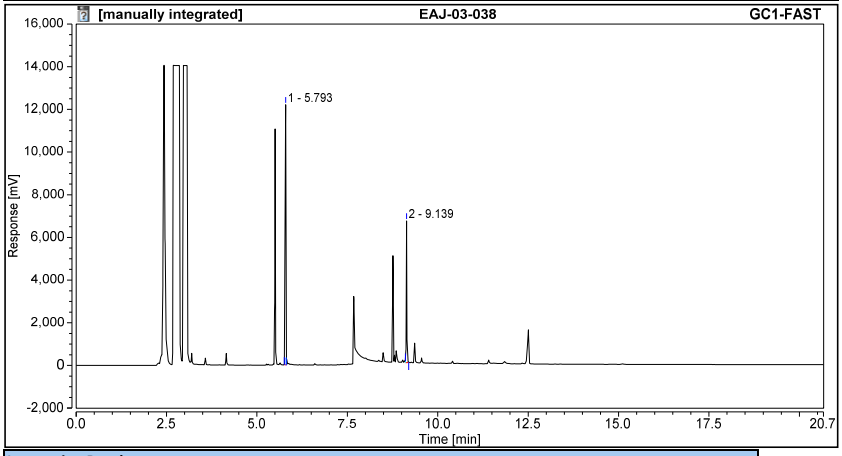
From *N,N*-diethylundec-10-enamide[4] (120 mg, 0.5 mmol) following **GP6**, to afford **5l** (RT = 9.139 min) in 25% GC yield (internal standard: dodecane, RT = 5.793 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-038**	*Run Time (min):*	**20.67**
Vial Number:	**8**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**18/Jun/20 09:55**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.793	244.278	12184.381	66.14	64.72
2		9.139	125.039	6642.170	33.86	35.28
Total:			**369.317**	**18826.551**	**100.00**	**100.00**

1-Bromododecane (5m)

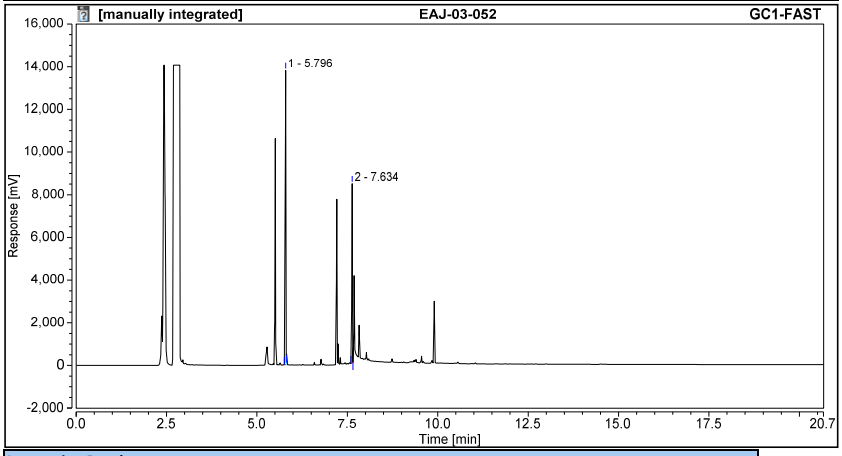
From 11-bromo-1-undecene (110 µL, 0.5 mmol) following **GP6**, to afford **5m** (RT = 7.634 min) in 21% GC yield (internal standard: dodecane, RT = 5.796 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-052**	*Run Time (min):*	**20.67**
Vial Number:	**5**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**30/Jun/20 11:47**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.796	297.314	13792.195	64.92	62.16
2		7.634	160.657	8397.074	35.08	37.84
Total:			**457.971**	**22189.270**	**100.00**	**100.00**

Dimethyl(phenyl)(propyl)silane (5n)

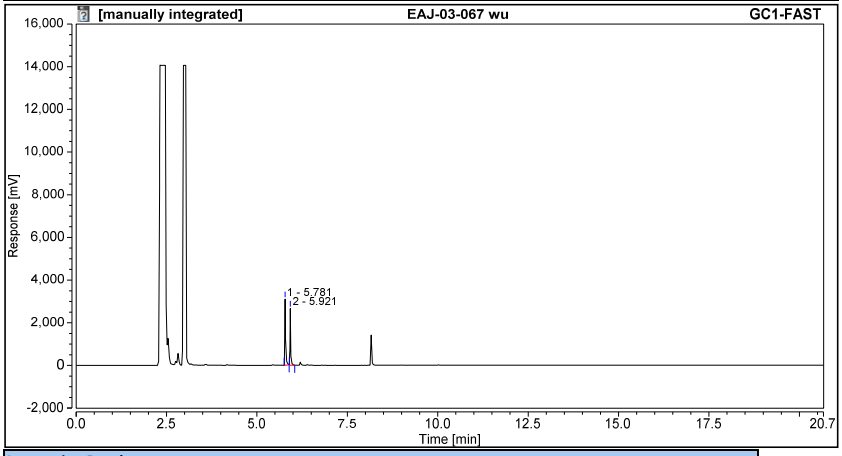
From dimethylphenylvinylsilane (91 µL, 0.5 mmol) following **GP6**, to afford **5n** (RT = 5.921 min) in 40% GC yield (internal standard: dodecane, RT = 5.781 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-067 wu**	*Run Time (min):*	**20.67**
Vial Number:	**3**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**10/Jul/20 09:32**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.781	62.789	3092.023	52.91	53.80
2		5.921	55.872	2655.523	47.09	46.20
Total:			**118.661**	**5747.546**	**100.00**	**100.00**

1-(3,4-Methylenedioxyphenyl)butane (5o)

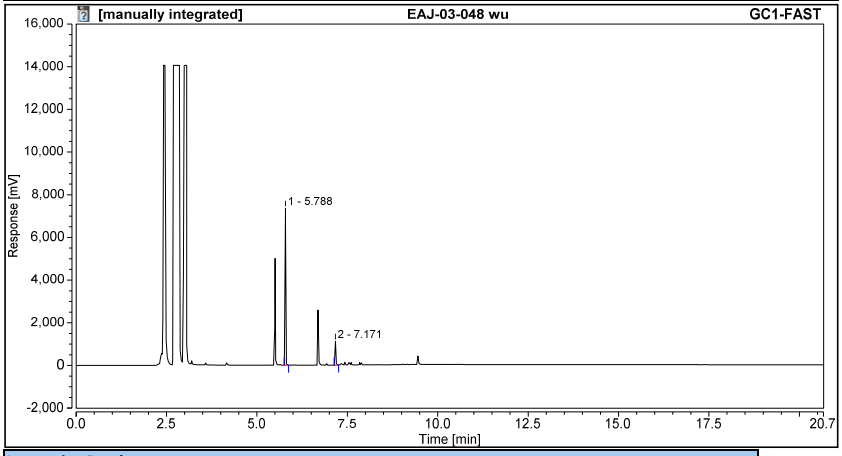
From safrole (74 µL, 0.5 mmol) following **GP6**, to afford **5o** (RT = 7.171 min) in 11% GC yield (internal standard: dodecane, RT = 5.788 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-048 wu**	*Run Time (min):*	**20.67**
Vial Number:	**3**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**24/Jun/20 12:44**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		5.788	129.236	7350.349	83.61	86.80
2		7.171	25.339	1117.947	16.39	13.20
Total:			**154.575**	**8468.296**	**100.00**	**100.00**

2-((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl dodecanoate (5p)

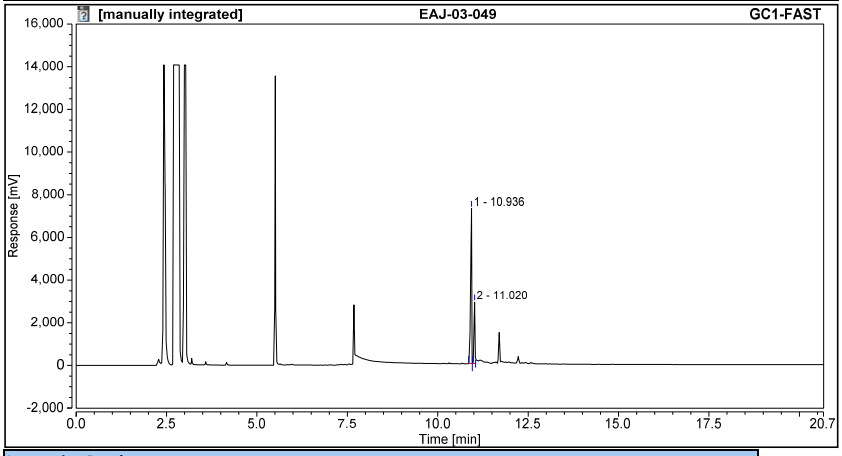
From (−)-nopyl undec-10-enoate[4] (166 mg, 0.5 mmol) following **GP6**, to afford **5p** (RT = 11.020 min) in 31% GC yield (internal standard: tetracosane, RT = 10.936 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-049**	*Run Time (min):*	**20.67**
Vial Number:	**5**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**24/Jun/20 13:43**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		10.936	261.704	7258.572	74.87	71.69
2		11.020	87.835	2865.993	25.13	28.31
Total:			**349.539**	**10124.565**	**100.00**	**100.00**

3,7-Dimethyloct-6-en-1-yl dodecanoate (5q)

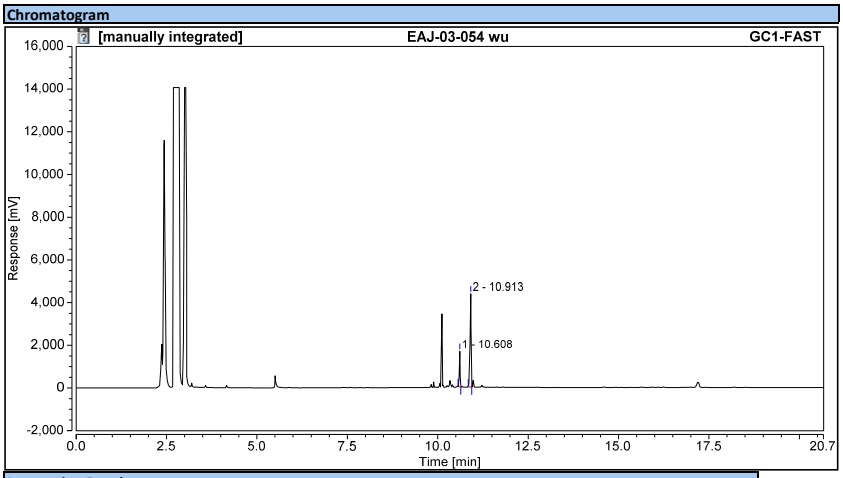
From β-citronellyl undec-10-enoate[4] (169 mg, 0.5 mmol) following **GP6**, to afford **5q** (RT = 10.608 min) in 12% GC yield (internal standard: tetracosane, RT = 10.913 min).

Chromatogram and Results

Injection Details

Injection Name:	**EAJ-03-054 wu**	*Run Time (min):*	**20.67**
Vial Number:	**5**	*Injection Volume:*	**1.00**
Injection Type:	**Unknown**	*Channel:*	**GC1_FID**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**GC1-FAST**	*Bandwidth:*	**n.a.**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**26/Jun/20 08:49**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mV*min	Height mV	Relative Area %	Relative Height %
1		10.608	38.385	1667.138	21.17	27.60
2		10.913	142.897	4373.495	78.83	72.40
Total:			**181.282**	**6040.634**	**100.00**	**100.00**

10. References

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4

Preparation of 2-Alkylated Tetrahydrofurans and Tetrahydropyrans via a Radical Pathway

Unpublished results

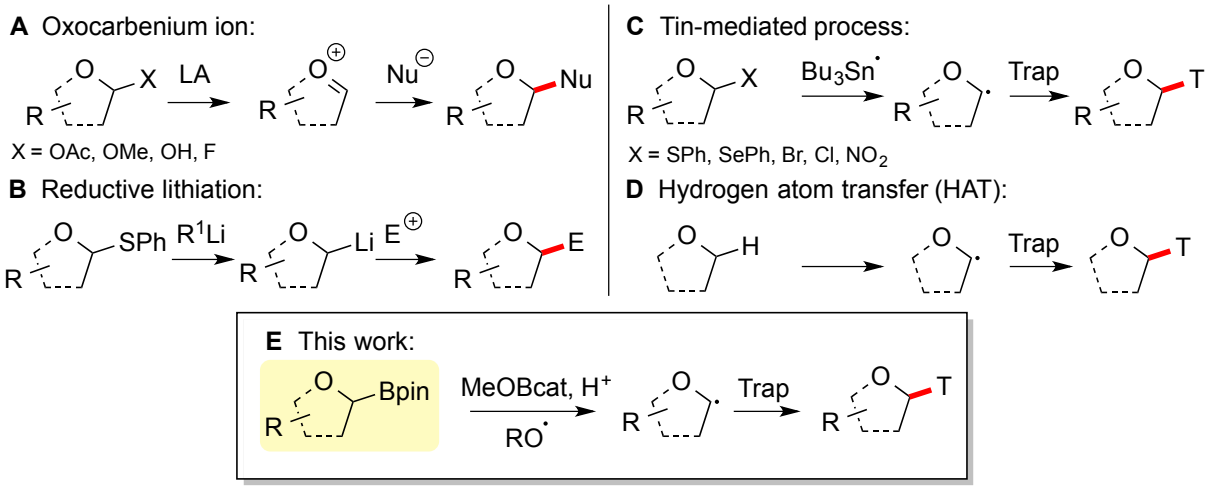
4. Preparation of 2-Alkylated Tetrahydrofurans and Tetrahydropyrans via a Radical Pathway

4.1 Introduction

Cyclic ethers such as tetrahydrofurans (THF) and tetrahydropyrans (THP) derivatives exist widely in natural products and exhibit a broad range of biological activity.[1] Besides their ubiquity in biologically active compounds, the challenges associated with the synthesis of such ring systems have attracted the interest of synthetic chemists. Most of the synthetic approaches to cyclic ethers are based on intramolecular C—O bond formation, which proceeds through reactions between a nucleophilic oxygen and an electrophilic carbon center.[2,3,4,5,6] Additionally, numerous methods based on radical cyclization have been developed involving addition of alkoxy,[6,7,8] 1-alkoxyalkyl,[9,10,11,12] and alkyl radicals to alkenes.[6] Alternatively, reaction of electrophilic alkene radical cations formed by single-electron oxidation with alcohol nucleophiles has been reported.[13,14,15,16,17] Moreover, the development of synthetic methods to functionalize the α-position of saturated cyclic ethers have attracted much attention. The most extensively used approach for the preparation of substituted THF and THP is the nucleophilic addition to an oxocarbenium ion formed by treatment with a Lewis acid, typically $BF_3.Et_2O$, TMSOTf, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, $AlCl_3$ or $SnBr_4$ (Scheme 1, **A**).[18,19,20,21,22,23,24,25] In contrast, the use of cyclic ethers as nucleophilic species has been exploited for the preparation of 2-substituted THF and THP. For instance, Cohen investigated the formation of lithiated intermediates by reductive lithiation of phenyl thioethers with aromatic radical anions (Scheme 1, **B**).[26] However, while the versatility of this method has been shown in the preparation of 2-functionalized THP derivatives, only three exemples of reductive lithiation of 2-(phenylthio)tetrahydrofurans were reported,[27] as a result of the rapid decomposition of unsubstituted THF with alkyllithium to generate ethane and lithium ethenolate.[28,29] Besides, the generation and functionalization of radicals from 2-substituted cyclic ethers (e.g. from phenylthio, phenylselenide, halogen or nitrile functional groups) have been well documented using tin-mediated radical chain reactions, with wide applications in C-glycosylation reactions (Scheme 1, **C**).[30,31,32,33,34,35,36,37] However, since tin reagents exhibit several problems such as high toxicities, costs, laborious purification processes and storages, alternative strategies have been developed to prevent its use, notably in the pharmaceutical sector.[38] Recently, the use of free radical oxidative coupling

strategies and single electron transfer approaches have emerged as powerful tools for the α-functionalization of saturated cyclic ethers. In this context, great progress has been achieved in the oxidative metal-catalyzed C—C bonds functionalization of α-C—H bonds (Scheme 1, **D**).[39,40,41,42,43,44] Although various metal-free oxidative methods have been developed,[45,46,47,48] these transformations suffer from low selectivity, harsh conditions, over oxidation, low efficiency and low tolerance to functional groups. In recent years, the use of visible-light induced methods has attracted significant interest due to their mild reaction conditions.[49] A more detailed overview of the precedent literature on the generation of 1-alkoxyalkyl radicals is disclosed in Chapter 5.

Herein, we wish to report a complementary approach for the regioselective α-functionalization of cyclic ethers using a practical and operationally simple protocol. Our long-standing interest for the generation of radicals from organoboron species[50,51,52,53,54,55,56,57] prompted us to investigate the use of pinacol boronic ester for the preparation of alkylated cyclic ethers. In a recent report, we developed mild reaction conditions for the radical C—C and C—X bonds functionalization of alkyl and α-haloalkyl radicals generated from pinacol boronic esters (R–Bpin).[58] This approach involves an *in situ* boron-transesterification of the pinacol boronic ester with a substoichiometric amount of catechol methyl borate (MeO–Bcat) to form the radical active catechol boronic ester specie (R–Bcat). On this basis, we examined a regioselective method to generate 1-alkoxyalkyl radicals starting from stable 1-alkoxyalkyl pinacol boronic esters, which are conveniently prepared through a C—H borylation/hydrogenation sequence (Scheme 1, **E**).

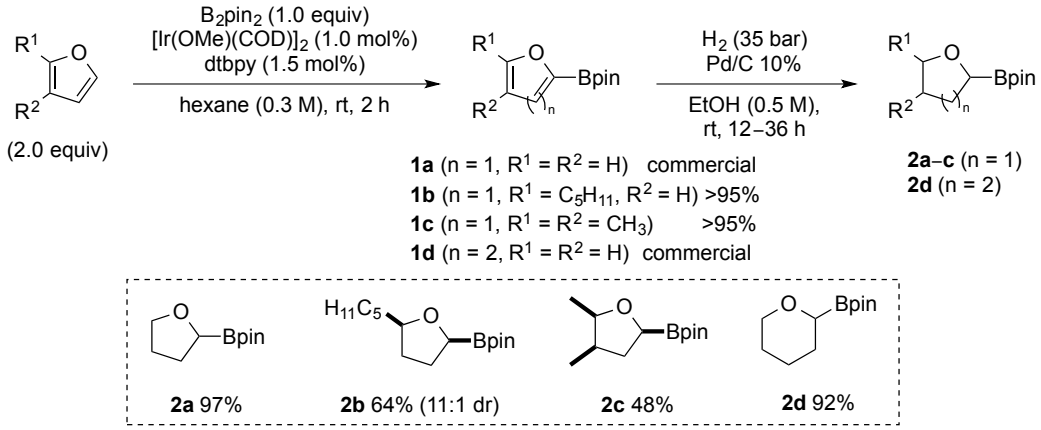


Scheme 1. Synthetic approaches for the α-functionalization of THF and THP

4.2 Results and discussion

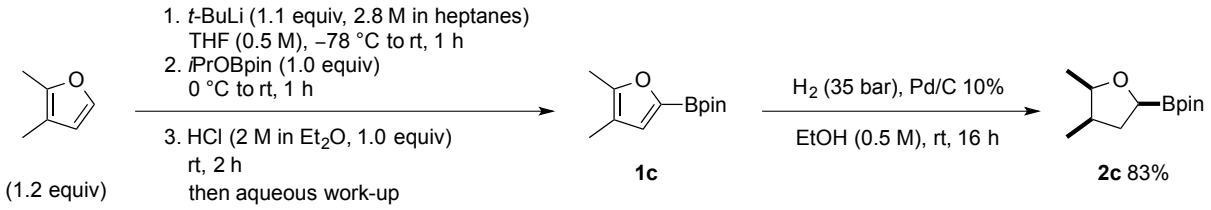
4.2.1 Synthesis of radical precursors

A two-step protocol was examined for the synthesis of 1-alkoxyalkyl pinacol boronic esters **2a**–**c**. First, a reported iridium-catalyzed borylation of heteroarenes was considered for the synthesis of furyl boronates **1b** and **1c** (Scheme 2).[59] High yields were obtained – based on the bis(pinacolato)diboron reagent – but contamination by boric acid pinacol ester (pinB–OH) could not be circumvented (10–20% of pinB–OH determined by ^{1}H NMR). Next, palladium-catalyzed hydrogenation of the boronate intermediates was performed to give **2a**–**c** in moderate to excellent yields (Scheme 2). In accordance with the literature,[60] high diastereoselectivities in favor of the *cis* products were detected for 2,5- and 2,3,5-substituted THF **2b** and **2c** (dr ≥ 11:1). Then, we turned our attention to the preparation of THP-containing pinacol boronic ester **2d**. Palladium-catalyzed hydrogenation of the commercially available 3,4-dihydro-2*H*-pyran-6-boronic acid pinacol ester delivered the corresponding saturated THP **2d** in high yield, emphasizing the potential of the sequence as an alternative to the commercially expensive **2d**.



*Scheme 2. Synthesis of THF and THP-containing pinacol boronic esters **2a–d** (yield of isolated product)*

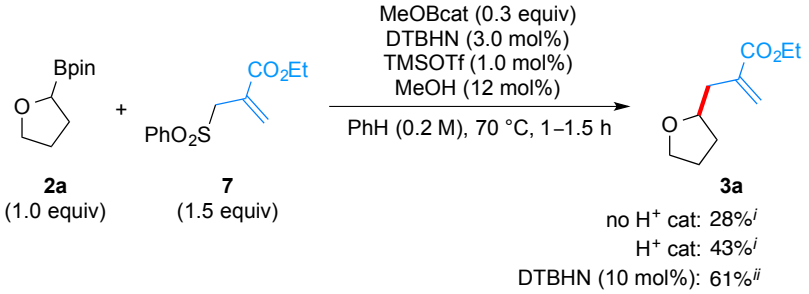
Eventually, a slightly different route towards **2c** was investigated. First, **1c** was prepared by lithiation of the 2,3-dimethylated furan followed by treatment with isopropoxy pinacol boronic ester (*i*PrO–Bpin) and subsequent protonolysis of the corresponding ate complex with HCl. The crude residue was then engaged in the palladium-catalyzed hydrogenation step, affording **2c** in excellent overall yield (Scheme 3).



*Scheme 3. Alternative borylation/hydrogenation sequence to furnish **2c** (yield of isolated product on a 24 mmol scale)*

4.2.2 Optimizations of the radical deboronative alkylation chain process

For our initial studies, the radical allylation of **2a** with the allylic sulfone **7**[61] initiated by di-*tert*-butylhyponitrite (DTBHN)[62] was investigated. In analogy with previous results obtained from alkyl pinacol boronic esters,[58] initial experiments supported the idea that acid catalysis accelerates the transesterification process (Scheme 4). It was further noticed that only a substoichiometric amount of MeO–Bcat was necessary to run the reaction to completion. Additionally, neither portionwise addition of DTBHN nor larger amount of radical trap significantly increased the yield. These results suggest a fast boron-transesterification, supporting the rather short reaction times observed.

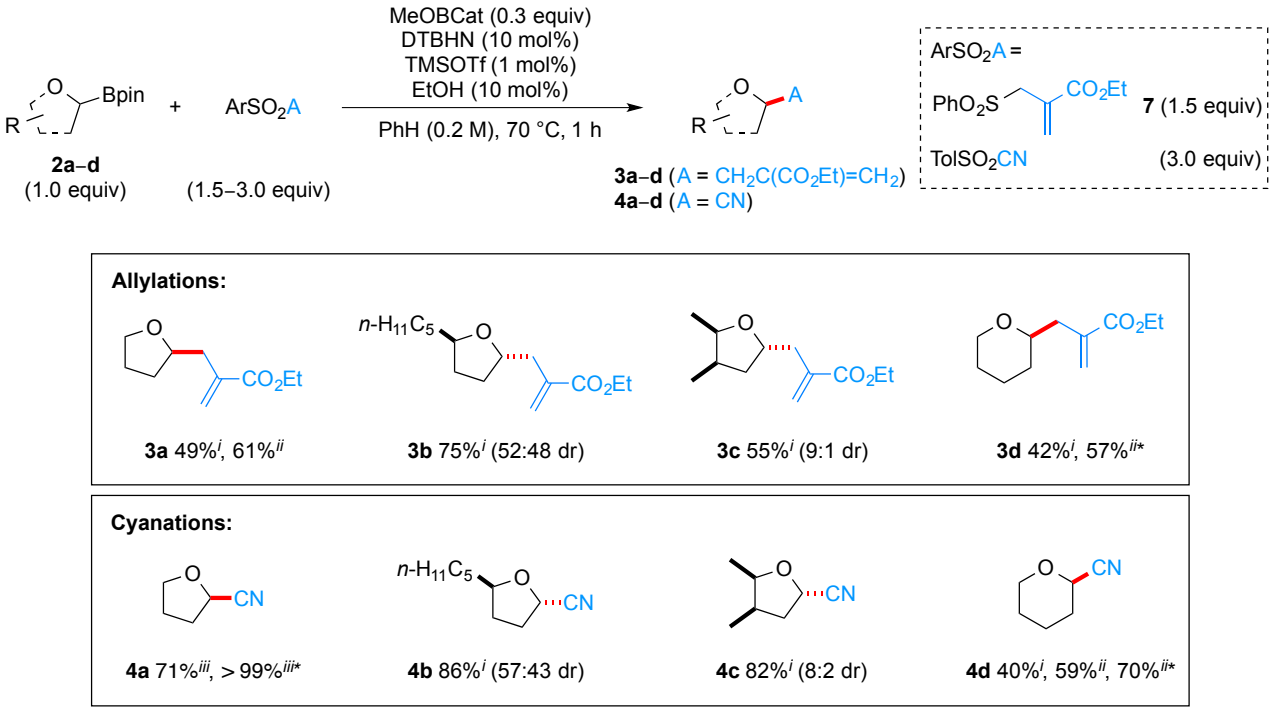


*Scheme 4. Optimization of the radical deboronative allylation of **2a**. [i] Yield of isolated product (1.0 mmol scale). [ii] GC yield (0.4 mmol scale)*

4.2.3 Scope of the radical deboronative alkylation chain process

Under the optimized conditions, the allylation of divers cyclic ethers **2a–d** was tested (Scheme 5). The reaction proceeded smoothly starting from tetrahydrofuran derivatives. Substitution at the 4-position of the ring did not deliver diastereoselectivity control, while precursor **2c** substituted at positions 3 and 4 induced good diastereoselectivity. This method

was also applied to the synthesis of the allylated tetrahydropyran **3d**, which was obtained in moderate yield albeit three equivalents of **7** were required in this case. Besides, we sought to explore the deboronative radical cyanation of **2a–d**. As expected, the cyanated compounds **4a–d** were obtained in good to high yields (70–99%) with diastereoselectivities matching those observed in allylation reactions.

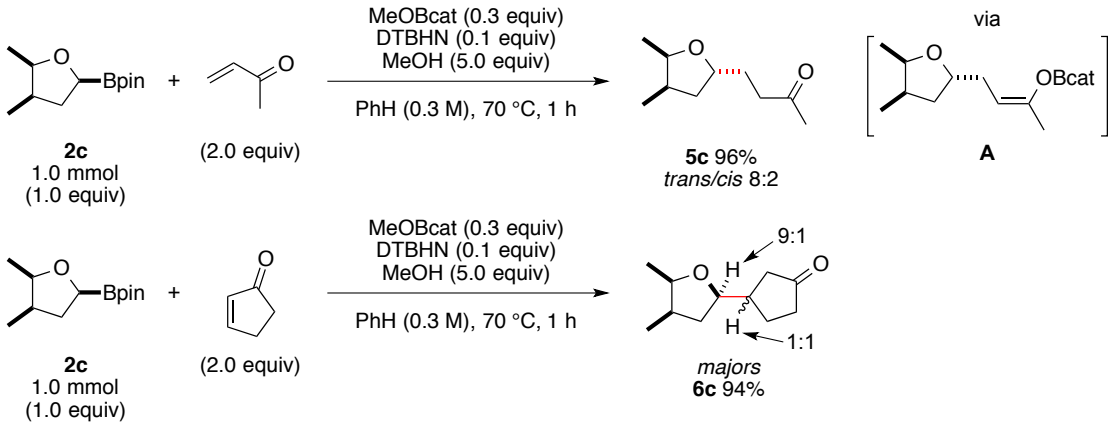


*Scheme 5. Radical deboronative allylation and cyanation. [i] Yield of isolated product (1.0 mmol scale). [ii] Yield determined by quantitative GC analysis (0.4 mmol scale). [iii] ^{1}H NMR yield (0.4 mmol scale). *The amount of radical trap was doubled*

4.2.4 Going further – Radical deboronative conjugate addition to enones

As shown by the preparation of **3c** and **4c**, tetrahydrofurans substituted at the C-3 and C-4 positions of the ring showed significant increase in diastereocontrol. This diastereoselective outcome was further demonstrated in a deboronative radical conjugate addition of **2c** with both methyl vinyl ketone and 2-cyclopentenone as coupling partners (Scheme 6). As expected, hydroalkoxymethylated tetrahydrofurans **5c** and **6c** were accessed in excellent yields and with good *trans* diastereoselectivity. In this sequence, the use of five equivalent of MeOH was critical for the chain process since hydrolysis of the boron-enolate **A**, which results from the

trapping of the enolyl radical with the catechol boronic ester intermediate, is responsible for MeO–Bcat recycling (Scheme 6, see Chapter 5 for mechanistic details).



Scheme 6. Radical Deboronative Conjugate Addition to Enones (yield of isolated product on a 1.0 mmol scale)

4.3 Conclusion

In summary, we have developed a practical and operationally simple protocol for the regioselective functionalization of cyclic ethers. This method involves an *in situ* boron-transesterification of a pinacol boronic ester with substoichiometric amount of MeO–Bcat to generate the highly reactive catechol boronic ester. This approach allows the use of stable and easy-to-handle boronic acids that are synthetically accessible. A variety of THF and THP ring systems were successfully alkylated and good diastereoselectivities were observed when using 2,3-disubstituted THF ring systems. Further investigations to generate 1-alkoxyalkyl radicals from easily available pinacol boronic esters are discussed in Chapter 5.

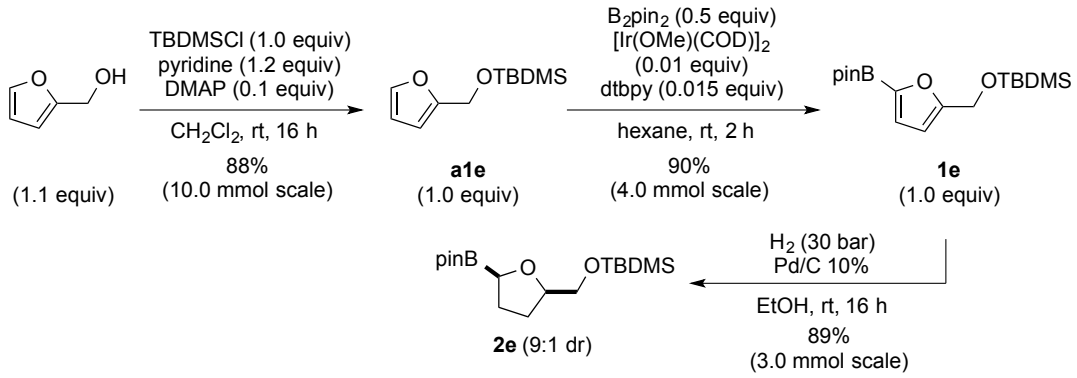
4.4 Additional Results

4.4.1 Expansion of the radical deboronative alkylation chain process

4.4.1.a Application to a functionalized tetrahydrofuran

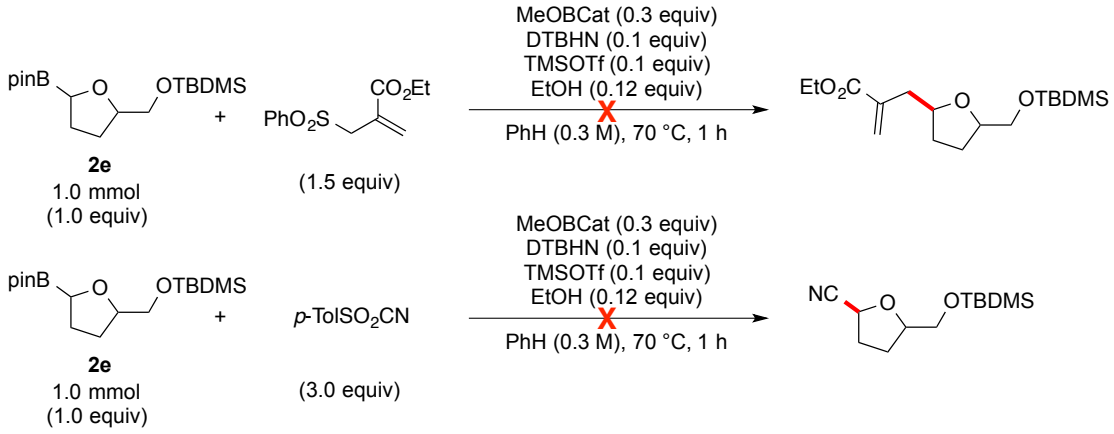
Having developed suitable reaction conditions for the radical deboronative alkylations of cyclic ethers, we sought to explore the limitations of the transformation in terms of chemical functionalities. In this context, we selected the silylated derivative **2e**, easily prepared with good

diastereoselectivity in favor of the *cis* product by mean of protection of the furfuryl alcohol, iridium catalyzed borylation of the resulting silylated product **a1e**, and subsequent hydrogenation of **1e** (Scheme 7).



*Scheme 7. Preparation of the radical precursor **2e** (yield of isolated product)*

However, all attempts to perform the radical deboronative alkylation of **2e** failed (Scheme 8). The deboronative allylation furnished only traces of alkylated product while deboronative cyanation did not allow detection of the cyanated ring. We anticipated that acidic conditions could be detrimental to the silyl group when heated at 70 °C. Therefore, we set up the radical deboronative allylation in absence of acid catalysis, but no product could be detected either.



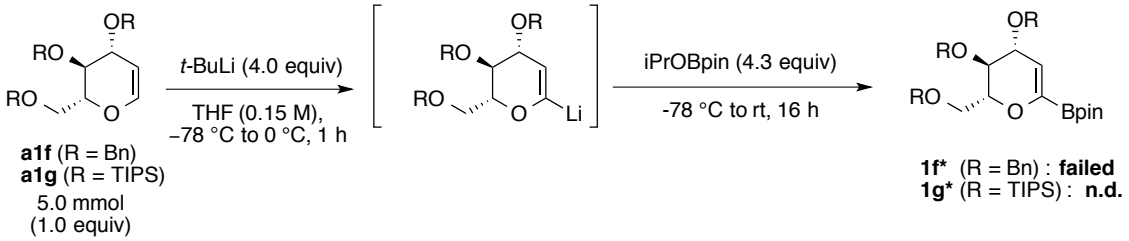
*Scheme 8. Radical deboronative alkylations of **2e***

4.4.1.b Application to a carbohydrate derivative

Moving forward, we wanted to illustrate the potential of the radical deboronative transformation on more complex structures containing a THP core. On this basis, we turned our

attention to a carbohydrate derivative. Because of its availability, D-glucal was selected for further investigations.

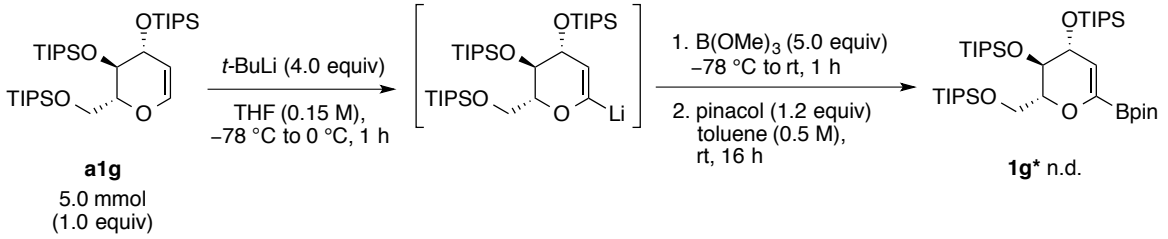
Our initial attention focused on the synthesis of a suitable protected D-glucal pinacol boronic ester. After simple benzyl protection, a reported strategy involving the reaction of 1-lithiated intermediate **a1f** with *i*PrO–Bpin was followed for the preparation of the borylated alkenyl sugar derivative **1f** (Scheme 9).[66] Interestingly, the formation of **1f** was not observed and most of the benzylated D-glucal **a1f** was recovered.



*Scheme 9. Attempted borylation of D-glucal **a1f–g**. *Not characterized*

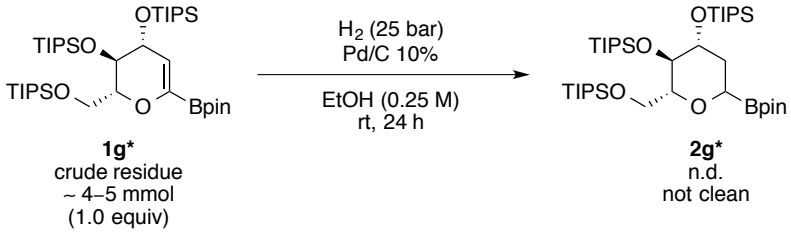
After a careful search in the literature, it turned out that the use of silyl protecting groups would be more suitable to treatment with *tert*-butyllithium.[66,67] Therefore, the tri-*O*-TIPS-protected glucal **a1g** was engaged in the borylation protocol (Scheme 9) and its full conversion into the boronic ester **1g** was observed. However, spectral data analysis of the crude residue indicated the presence of another boronic ester, tentatively assigned as *t*-Bu–Bpin (^{11}B NMR: δ 34 ppm). Attempts to purify the product by different methods (i.e., column chromatography and Kugelrohr distillation techniques) resulted in partial separation and/or decomposition.

To prevent the possible formation of *t*-Bu–Bpin, we decided to approach the synthesis of **1g** using a stepwise protocol, that is, the formation of boronic acid **b1g** followed by transesterification with pinacol (Scheme 10). Although other research groups have shown that this method could to lead to complex reaction mixtures,[66,68] the formation of the desired borylated alkenyl 3,4,6-tri-*O*-TIPS-D-glucal **1g** was detected. Unfortunately, it turned out that this approach did not prevent the formation of *t*-Bu–Bpin.



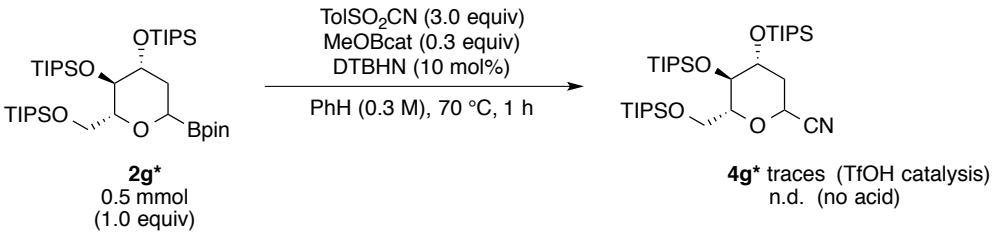
*Scheme 10. Sequential approach for the borylation of D-glucal **a1g**. *Not characterized*

Hence, we engaged the crude residue as such in the next step and hydrogenation of **1g** proceeded smoothly to generate the radical precursor **2g** (Scheme 11). At this stage, purification processes to remove the *t*-Bu–Bpin formed during the borylation sequence remained unsuccessful and **2g** could not be isolated in sufficient purity. Pleasingly, the formation of only one diastereomer of **2g** was detected although its relative configuration has not been confirmed yet.



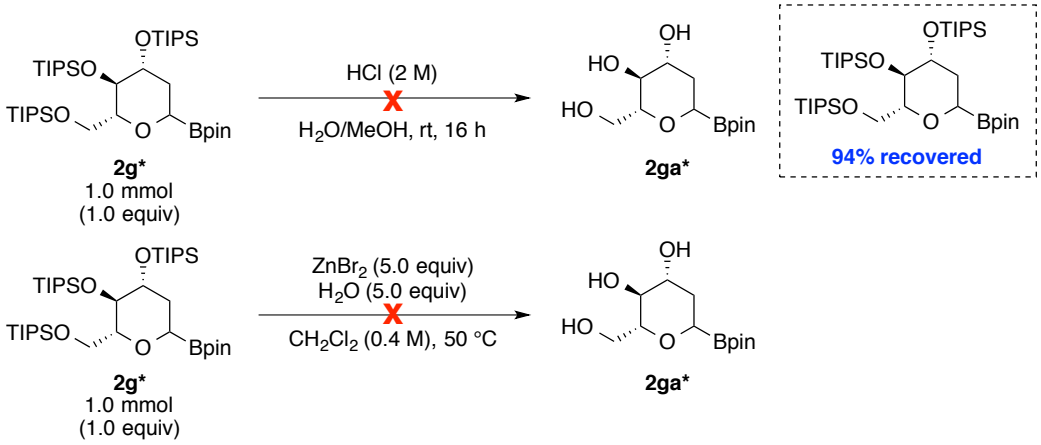
*Scheme 11. Hydrogenation of **1g** to furnish the radical precursor **2g**. *Not characterized*

Considering the difficulties encountered with product isolation, the crude residue **2g** was engaged as such in the radical deboronative cyanation reaction. While full consumption of **2g** was observed after one hour, only traces of the cyanated product **4g** were detected (Scheme 12). The failing of the transformation can be explained by the acidic conditions responsible for partial deprotection of the TIPS protecting groups. Indeed, when carried out under non-acidic conditions, cyanation of the sugar derivative proved successful although we could not separate **4g** from *t*-Bu–Bpin.



*Scheme 12. Radical deboronative cyanation of **2g** to furnish **4g**. *Not characterized*

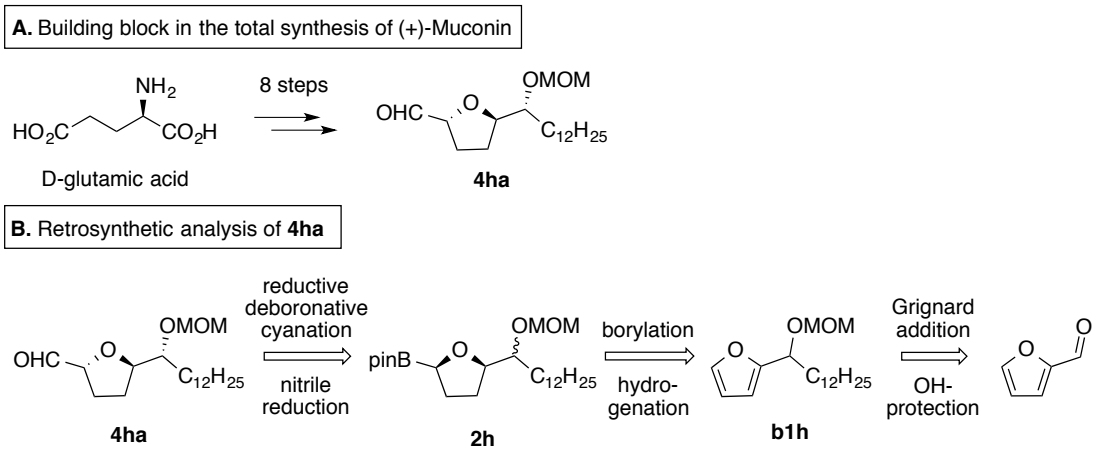
In view of the aforementioned results, we sought to deprotect the D-glucal pinacol boronic ester **2g** prior to the radical deboronative cyanation reaction. Additionally, we assumed that the formation of the polar product **2ag** would allow easier separation from the less polar *t*-Bu–Bpin. Considering the known reactivity of boronic esters towards fluoride, we chose to perform the deprotection under acidic conditions. However, attempts to deprotect the silyl-protected D-glucal boronic ester **2g** using either 2 M HCl solution in a mixture of water and methanol or *in situ* generated HBr were not successful with one resulting in no reaction and the other in product decomposition (Scheme 13).



*Scheme 13. TIPS-deprotection of **2g** to furnish **2ga**. *Not characterized*

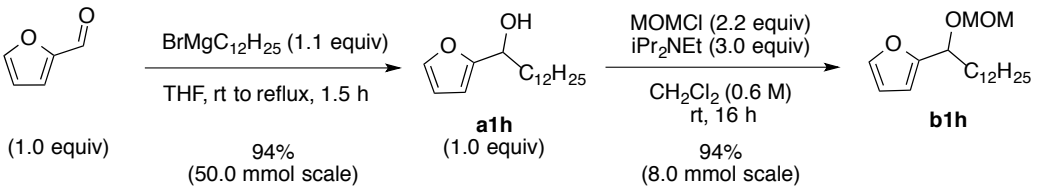
4.4.1.c Preparation of a key building block in the total synthesis of (+)-Muconin

Next, the potential of the radical deboronative alkylation was evaluated on the synthesis of aldehyde **4ha**, a key building block in the total synthesis of (+)-Muconin reported by Yang and Kitahara.[71] In their approach, **4ha** was accessed in 12% overall yield over eight steps from D-glutamic acid (Scheme 14, **A**). Herein, we wish to report an alternative route to **4ha** through a six steps synthetic pathway (Scheme 14, **B**). In this approach, the aldehyde would be generated by radical deboronative cyanation of a pinacol boronic ester **2h** and reduction of the resulting nitrile derivative. The corresponding boronic ester would be accessed by borylation of furan **b1h** and subsequent hydrogenation. Finally, furan **b1h** would be readily prepared by Grignard addition of dodecyl magnesium bromide to furfural followed by alcohol protection.



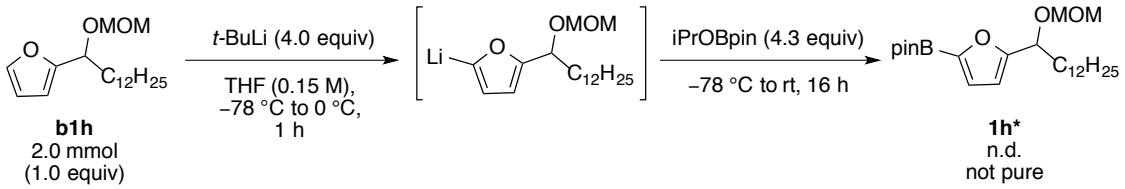
*Scheme 14. (A) Route to **4ha** in the total synthesis of (+)-Muconin. (B) Retrosynthetic analysis of **4ha** using a key radical deboronative cyanation reaction*

As shown in Scheme 15, furan **b1h** was easily accessed using the aforementioned two steps protocol. Next, **b1h** was engaged in the borylation sequence.



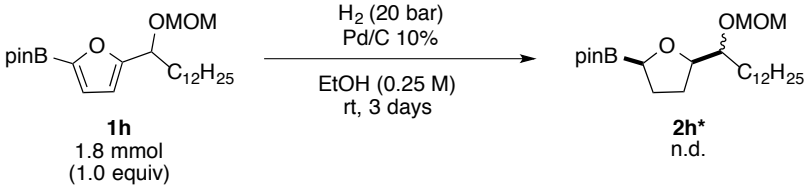
*Scheme 15. Preparation of **b1h** from furfural (yield of isolated product)*

The formation of compound **1h** was detected but we could not isolate it in an acceptable purity (Scheme 16). Indeed, as observed in the synthesis of **1g** (Scheme 9), the predominance of by-products could not be prevented and the purification processes proved ineffective. In this case, the presence of the methoxymethyl ether (MOM) protecting group (considered as an *ortho* directing metalation group) can promote the formation of complex mixtures of α-lithiated *O*-methoxymethyl derivatives and benzylic-lithiated regioisomers.[72]



*Scheme 16. Borylation of **b1h** to furnish **1h**. *Not characterized*

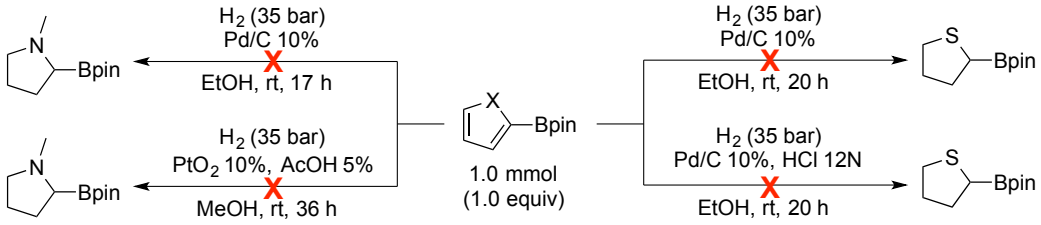
Therefore, **1h** was engaged as such in the hydrogenation step (Scheme 17). Although detection of **2h** was possible by ^{1}H NMR analysis of the crude residue, spectra data also suggested predominant formation of side-products presumably resulting from side chain removal or ring opening.[73] Since many difficulties were encountered with the synthesis of these more complex radical precursors, we turned our attention to other avenues of investigations. Nonetheless, the exploration of other borylation procedures are underway in order to obtain the pure radical precursor **1h**.



*Scheme 17. Hydrogenation of **1h** to furnish **2h**. *Not characterized*

4.4.2 Reactivity of cyclic α-amino and α-sulfur radicals

Hereof, we sought to expand this methodology to the generation of α-amino and α-sulfur radicals. Hence, commercially available thiophene-2-boronic acid pinacol ester and 1-methyl-2-pyrroleboronic acid pinacol ester were subjected to palladium catalyzed hydrogenation (Scheme 18). As expected by the possible poisoning of the catalyst by either sulfur or nitrogen containing compounds, the commonly used hydrogenation reaction conditions (i.e. used for furan derivatives) did not provide any reaction and the pinacol boronic ester precursors were fully recovered.[74] Unfortunately, when we applied reported reaction conditions carried out in the presence of acid, the hydrogenated compounds were also not detected and the starting unsaturated heterocyclic systems were recovered (Scheme 18).[75] After a careful examination of the literature, we did not find any example of hydrogenation of either thiophene or pyrrole containing boronic ester groups. This synthetic limitation did not allow us to go further with this project. A new strategy must be design for the preparation of cyclic 1-alkoxyamino and 1-alkoxysulfor pinacol boronic esters.

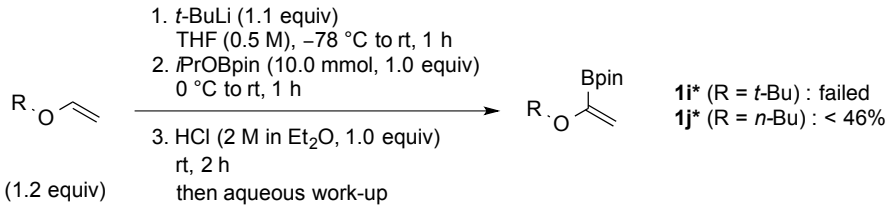


Scheme 18. Hydrogenation of 2-substituted thiophene and pyrrole pinacol boronic esters

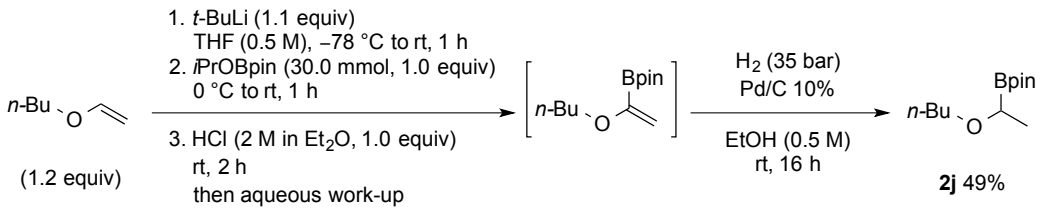
4.4.3 Application to acyclic 1-alkoxyalkyl pinacol boronic esters

4.4.3.a Preliminary results

Next, we wanted to explore the radical deboronative alkylation of acyclic 1-alkyxoalkyl pinacol boronic esters. On this basis, a borylation/hydrogenation sequence was also adopted for the preparation of the radical precursors **1i–j** (Scheme 19). The formation of *tert*-butylboronic acid pinacol ester (*t*-Bu–Bpin) was exclusively observed when *tert*-butyl vinyl ether was subjected to the borylation step, indicating that the hindrance induced by the two *tert*-butyl moieties of the vinyl ether derivative and of the lithiating species do not allow deprotonation to occur. Accordingly, this transformation was performed on *n*-butyl vinyl ether and the resulting borylated compound **1j** was detected, although decomposition of the crude residue after aqueous work-up occurred within minutes when left on the bench open to air. Therefore, a one pot protocol was envisaged in order to prevent decomposition of the reactive vinylic pinacol boronic ester intermediate, and **2j** was eventually obtained in fair yield over the two-steps sequence (Scheme 20).

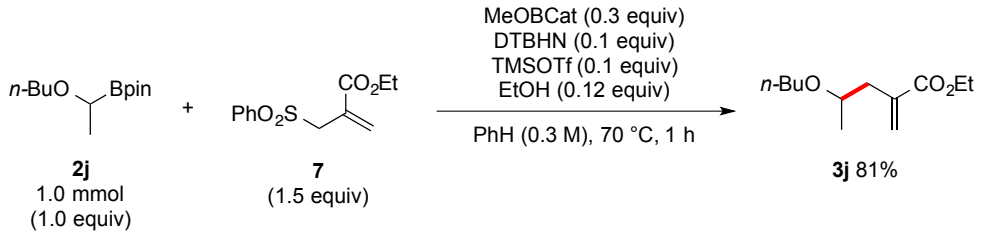


*Scheme 19. Borylation of acyclic vinyl ethers. *Not characterized*



*Scheme 20. One-pot borylation/hydrogenation sequence to furnish **2j** (yield of isolated product)*

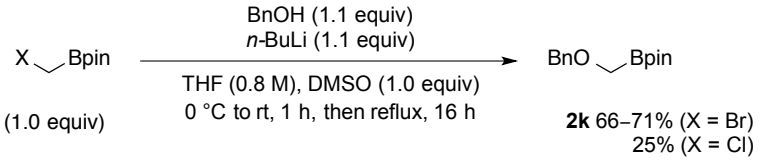
Pleasingly, the radical deboronative allylation of **2j** provided **3j** in 81% yield (Scheme 21). The outcome of this transformation encouraged us to investigate the generation of primary 1-alkoxyalkyl radicals.



*Scheme 21. Radical deboronative allylation of **2j** to furnish **3j** (yield of isolated product)*

4.4.3.b Going further – Toward a hydroalkoxymethylation process

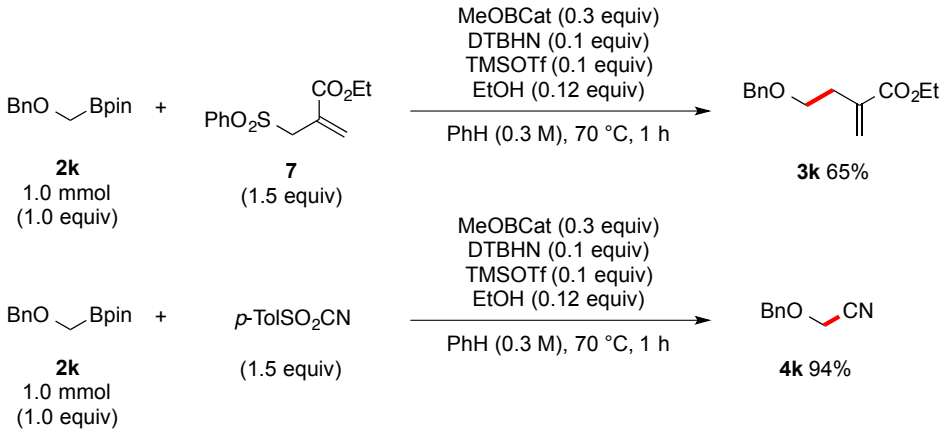
Hence, we decided to keep the benzyl protected alcohol which would allow further deprotection. This strategy relies on the preparation of the radical precursor **2k**, which proved readily accessible through a 1,2-metalate shift from the reaction of commercially available (bromomethyl)boronic acid pinacol ester ($BrCH_2Bpin$) and *in situ* generated lithium benzyloxide (Scheme 22).



*Scheme 22. Preparation of the radical precursor **2k** (yield of isolated product)*

Next, **2k** was subjected to the radical deboronative alkylations and the allylated and cyanated compounds **3k** and **4k** were obtained in 65% and 94%, respectively (Scheme 23). The successful application of the current methodology stimulated us to further explore a general

approach for the generation of 1-alkoxymethyl radicals, and study their synthetic utility (see Chapter 5).



*Scheme 23. Radical deboronative alkylation of **2k** to furnish **3k** and **4k** (yield of isolated product)*

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Experimental Part

Contents

1. General and instrumentation

Glassware and reaction techniques: Unless otherwise stated, all glassware was flame-dried, cooled under vacuum, and back-filled with nitrogen or argon; then the reactions were run under that inert atmosphere (atm) and additions of solids were performed under a positive pressure of that inert atm. Unless otherwise stated, all yields are isolated yields. Room temperatures (rt) were generally in the range 21–25 °C.

Solvents: Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), *n*-hexane and benzene (PhH) for reactions were filtered through a column of dried alumina under a positive pressure of argon. Ethanol (EtOH) for hydrogenation reactions was purchased (reagent grade, Aldrich) and used as such. *N,N*-Dimethylformamide (DMF) was purchased from Aldrich (anhydrous, 99.8% [CAS = 68-12-2]) and used as such. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. All water used for solutions, quenches, and aqueous extractions was deionized water.

Reagents and chemicals: All reagents and chemicals used were commercial and used without further purification unless specified below. Compound **4a** was purchased from Combi-Blocks [CAS 14631-43-7] and used as reference for GC yield determination.

Column chromatography: All chromatographic purifications were flash (ca. 2–3 atm. of pressurized air) column chromatography (FCC) on silica gel (Macherey-Nagel Silica 60, 0.04 – 0.063 mm) and/or neutral aluminium oxide (CAMAG 507 – C – I neutral).

Thin layer chromatography (TLC): Silicycle glass backed TLC extra hard layer, 259 µm, 60 Å, F-254 Silica gel 60 Å (F-254) and *Macherey-Nagel* SIL G/UV254, 0.25 mm analytical plates were used for TLC. Revelation was done firstly by non-destructive visualization under a UV lamp (254 nm); destructive revelation was performed with staining solutions of either potassium permanganate ($KMnO_4$) or cerium molybdate (CAM) followed by heating.

NMR: The NMR experiments were performed on a Bruker Avance-300 spectrometer operating at a resonance frequency of 300.18 MHz for ^{1}H nuclei, 75.48 MHz for ^{13}C and 96 MHz for ^{11}B nuclei. ^{11}B NMR spectra were calibrated using $Et_2O.BF_3$ (0.0 ppm) as an external reference. Chemical shifts are reported in units of δ (ppm) using the internal standard residual $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR spectra and δ = 77.16 ppm for ^{13}C NMR spectra), TMS (δ = 0.00 ppm for ^{1}H NMR spectra and δ = 0.00 ppm for ^{13}C NMR spectra), C_6D_6 (δ = 7.16 ppm for ^{1}H NMR spectra and δ = 128.06 ppm for ^{13}C NMR spectra), or CD_2Cl_2 (δ = 5.32 ppm for ^{1}H NMR spectra and δ = 54.00 ppm for ^{13}C NMR spectra). Due to coupling to the quadrupolar ^{11}B and ^{10}B nuclei, the carbons linked to boron atoms generally give a broad signal in ^{13}C NMR and are

usually not detectable. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextuplet, m = multiplet, app = apparent. Referencing and common impurities were assigned by common standards.[1,2]

GC: GC analyses were carried out on a Thermo Electron Trace GC ULTRA instrument fitted with a Macherey-Nagel Optima delta-3-0.25 µm capillary column (20 m, 0.25 mm). Gas carrier: He 1.4 mL/min; injector: 220 °C split mode; detector: FID 280 °C, H2 35 mL/min, air 350 mL/min. Infrared spectra were recorded on a Jasco FT/IR-4700 Spectrometer and are reported in wave numbers (cm^{-1}).

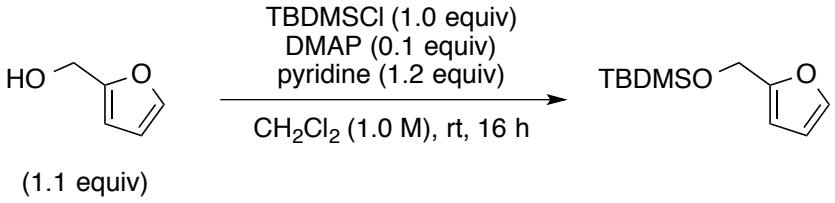
MS: HRMS analyses and elemental composition determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using Electron Spray Ionization (ESI) and Nanospray Ionization (NSI) mode at the University of Bern. When ESI and NSI was not sufficient to ionize the molecule, HRMS was performed at the University of Zürich with a Bruker maXis QTof high resolution mass spectrometer (APCI mode) and Thermo DFS (ThermoFisher Scientific) double-focusing magnetic sector mass spectrometer (EI and CI modes).

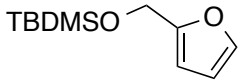
IR: Infrared spectra were recorded neat equipped with a diamond ATR System and are reported in wave numbers (cm^{-1}). Reported are the characteristic signals only (with decreasing wave number).

2. Experimental Procedures and Characterizations for the Synthesis of Reagents and Substrates

2.1 Protection of silyl protected a1e

tert-Butyl(furan-2-ylmethoxy)dimethylsilane (a1e)



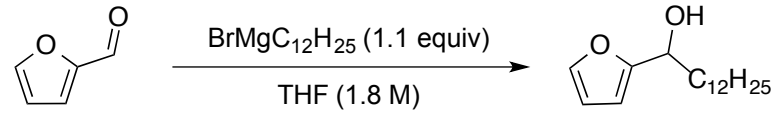


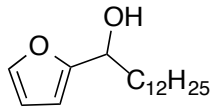
$C_{11}H_{20}O_2Si$
MW: 212.12

A one-neck, 50 mL round-bottom flask was charged with 2-furylmethanol (1.1 g, 11.0 mmol, 1.1 equiv), *tert*-butyldimethylsilyl chloride (1.5 g, 10.0 mmol, 1.0 equiv), pyridine (0.97 mL, 12.0 mmol, 1.2 equiv), 4-dimethylaminopyridine (122 mg, 1.0 mmol, 0.1 equiv) and dissolved in CH_2Cl_2 (6.0 mL, 1.0 M). The contents were stirred at rt for 16 h, then partitioned between EtOAc (10 mL) and water (10 mL). After phases separation, the aqueous phase was back-extracted with EtOAc (5 mL) and the collected ethereal phases were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford **a1e** as a yellow oil (1.86 g, 8.8 mmol, 88%). Spectral and physical data were in accordance with the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.26 – 6.18 (m, 1H), 4.64 (s, 2H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 142.0, 110.2, 107.2, 58.2, 25.9, 18.4, -5.3.

2.2 Synthesis of b1h

1-(Furan-2-yl)tridecan-1-ol (a1h)



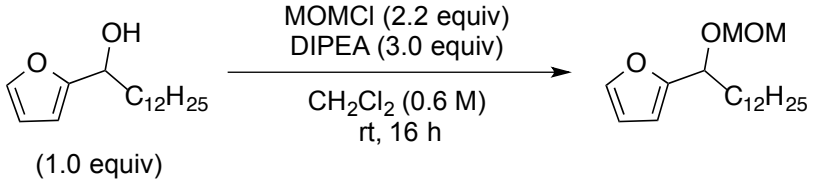


$C_{17}H_{30}O_2$
MW: 266.23

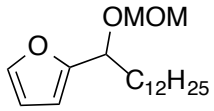
To a one-neck, 250 mL round-bottom flask equipped with a condenser was added 2-furaldehyde (4.15 mL, 50.0 mmol, 1.0 equiv) and THF (30 mL, 1.8 M). Dodecyl magnesium bromide (56.0 mL, 55.0 mmol, 1.1 equiv, 1.0 M in Et_2O) was added dropwise at rt and the resulting mixture were left to stir at this temperature for 1 h. The contents were then heated under reflux for 30 minutes, then cooled to rt and quenched by addition of sat. aq. NH_4Cl (50 mL). The contents were partitioned with TBME (50 mL), the two phases were separated and the aqueous phase was back-extracted with TBME (10 mL). The combined ethereal phases were washed with sat. aq. NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **a1h** as a white solid (12.5 g, 47 mmol, 94%). Spectral and physical data were in accordance with the literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.22 (dt, *J* = 3.3, 0.7 Hz, 1H), 4.66 (t, *J* = 6.8 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.49

– 1.38 (m, 1H), 1.37 – 1.16 (m, 20H), 0.88 (app t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 142.0, 110.2, 105.9, 68.0, 35.7, 32.1, 29.81, 29.78, 29.72, 29.67, 29.54, 29.50, 25.7, 22.8, 14.3.

2-(1-(Methoxymethoxy)tridecyl)furan (b1h)



(1.0 equiv)

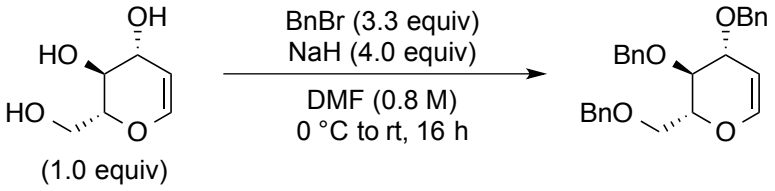


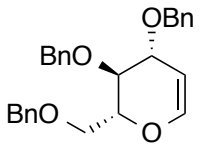
$C_{19}H_{34}O_3$
MW: 310.25

To a one-neck, 50 mL round-bottom flask was added **a1h** (2.13 g, 8.0 mmol, 1.0 equiv), CH_2Cl_2 (12.0 mL, 0.6 M) and DIPEA, *N,N*-diisopropylethylamine (4.2 mL, 24.0 mmol, 3.0 equiv). The contents were cooled to 0 °C and chloromethyl methyl ether, MOMCl (1.36 mL, 17.6 mmol, 2.2 equiv) was added dropwise. The reaction mixture was stirred at rt for 16 h, then diluted with CH_2Cl_2 (10 mL) and quenched by addition of sat. aq. $NaHCO_3$ (10 mL). The contents were stirred at rt for another hour and the two phases were separated. The aqueous phase was back-extracted with TBME (3×5 mL) and the collected organic phases were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 98:2) to afford **b1h** as a colorless oil (2.34 g, 7.5 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 1.8, 0.7 Hz, 1H), 6.32 (dd, J = 3.2, 1.8 Hz, 1H), 6.26 (dd, J = 3.2, 0.5 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.58 (t, J = 7.1 Hz, 1H), 4.53 (d, J = 6.8 Hz, 1H), 3.36 (s, 3H), 1.98 – 1.74 (m, 2H), 1.48 – 1.17 (m, 20H), 0.88 (app t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 142.4, 110.0, 108.1, 94.1, 71.1, 55.6, 34.2, 32.1, 29.80, 29.78, 29.72, 29.66, 29.52, 29.49, 25.8, 22.8, 14.3. IR (neat): 2922, 2853, 1150, 1097, 1030, 920, 734 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{34}O_3Na$ $[M+Na]^+$: 333.2400; found: 333.2397.

2.3 Synthesis of 3,4,6-Tri-*O*-protection of D-Glucal a1f–g

3,4,6-Tri-*O*-benzyl-D-glucal (a1f)

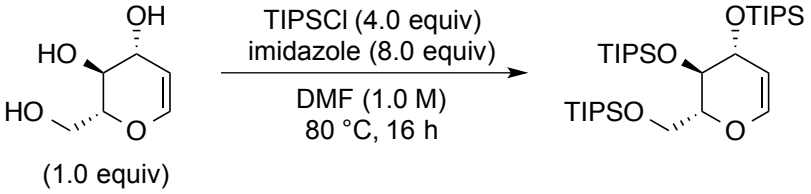


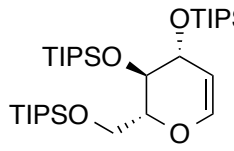


$C_{27}H_{28}O_4$
MW: 416.20

To a one-neck, 100 mL round-bottom flask containing D-glucal (1.46 g, 10.0 mmol, 1.0 equiv) in DMF (12.0 mL, 0.86 M) was added NaH (1.6 g, 40.0 mmol, 4.0 equiv) portionwise at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes before dropwise addition of benzyl bromide (4.13 mL, 33.0 mmol, 3.3 equiv) to the cooled solution. The resulting contents were allowed to warm to rt and left to stir for 16 h. The reaction mixture was carefully quenched by addition of cold water (30 mL), then diluted with EtOAc (30 mL) and the two phases were separated. The ethereal phase was washed with aq. sat. NH_4Cl (2×30 mL), sat. aq. NaCl (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 97:3) to afford **a1f** as a colorless oil (4.03 g, 9.7 mmol, 97%). Spectral and physical data were in accordance with the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 15H), 6.36 (dd, *J* = 6.1, 1.2 Hz, 1H), 4.81 (dd, *J* = 6.2, 2.7 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.62 – 4.45 (m, 5H), 4.18 – 4.11 (m, 1H), 4.01 (ddd, *J* = 8.2, 4.8, 3.1 Hz, 1H), 3.80 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.77 – 3.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 138.5, 138.3, 138.1, 128.6, 128.5, 128.5, 128.1, 127.92, 127.87, 127.8, 100.1, 76.9, 75.9, 74.5, 73.9, 73.7, 70.6, 68.7.

3,4,6-Tri-*O*-(triisopropylsilyl)-D-glucal (a1g)



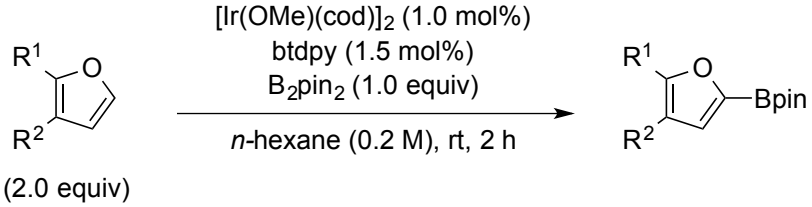


$C_{33}H_{70}O_4Si_3$
MW: 614.46

To a one-neck, 100 mL round-bottom flask equipped with a condenser was added D-glucal (2.92 g, 20.0 mmol, 1.0 equiv) and DMF (20 mL, 1.0 M). The contents were cooled to 0 °C and imidazole (10.9 g, 160 mmol, 8.0 equiv) and TIPSCl (17.1 mL, 80.0 mmol, 4.0 equiv) were successively added. The reaction mixture was left to stir at 80 °C for 16 h, then careful poured into an ice-cooled aq. sat. $NaHCO_3$ solution (40 mL). The resultant mixture was filtered through cotton and the aqueous phase was back-extracted with EtOAc

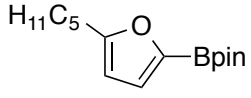
(2×20 mL). The combined extracts were washed with water (40 mL), sat. aq. NaCl (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/CH_2Cl_2 8:1) to afford **a1g** as a colorless oil (9.54 g, 15.5 mmol, 78%). Spectral and physical data were in accordance with the literature.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, *J* = 6.4 Hz, 1H), 4.80 (ddd, *J* = 6.6, 5.4, 1.7 Hz, 1H), 4.24 (ddt, *J* = 7.5, 3.6, 1.7 Hz, 1H), 4.12 – 4.02 (m, 2H), 3.95 (dt, *J* = 4.8, 1.8 Hz, 1H), 3.83 (dd, *J* = 11.3, 3.8 Hz, 1H), 1.16 – 0.98 (m, 63H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 100.5, 80.9, 70.4, 65.2, 62.2, 18.31, 18.25, 18.22, 18.15, 18.1, 12.7, 12.5, 12.2.

2.4 General Procedure 1 (GP1): Iridium catalyzed borylation of furans by B_2pin_2 to furnish 1b–c and 1e



A two-necks, 250 mL round-bottom flask was charged with $[Ir(OMe)(cod)]_2$ (1.0 mol%), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (1.5 mol%), and B_2pin_2 (1.0 equiv) in a glove-box. *n*-Hexane (0.2 M) and the corresponding heteroarene (2.0 equiv, 1.5 M in *n*-hexane) were successively added to the flask at rt. The contents were stirred for 2 h at this temperature and then quenched carefully by addition of water (50 mL). The two phases were separated and the aqueous phase was back-extracted with *n*-hexane (2×30 mL). The collected organic phases were washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

4,4,5,5-Tetramethyl-2-(5-pentyl-2-furyl)-1,3,2-dioxaborolane (1b)

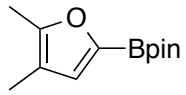


$C_{15}H_{25}BO_3$
MW: 264.19

From 2-pentylfuran (2.39 mL, 15.0 mmol) following **GP1**. The crude residue was purified by Kugelrohr distillation (141 – 144 °C, 2.4 mbar) to afford **1b** as an orange oil (2.0 g, 7.6 mmol, > 95%$^+$).[§] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 2.70 – 2.65 (m, 2H), 1.71 – 1.61 (m, 2H), 1.34 – 1.29 (m, 16H), 0.89 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 124.7, 105.9, 84.0, 31.5, 28.3, 27.7, 24.7, 22.4, 14.0. ^{11}B NMR (96 MHz, $CDCl_3$) δ 27.0, 22.5[§]. IR (neat): 2927, 1532, 1344, 1315, 1144, 1109, 1013, 965, 854,

786, 691, 603 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{25}O_3BNa$ $[M+Na]^+$: 287.1789; found: 287.1781. §Contaminated with pinBOH.[7] +Yield based on B_2pin_2.

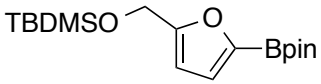
2-(4,5-Dimethylfuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1c)



$C_{12}H_{19}BO_3$
MW: 222.14

From 2,3-dimethylfuran (2.11 mL, 19.8 mmol) following **GP1**. The crude residue was purified by Kugelrohr distillation (148 – 151 °C, 2.4 mbar) to afford **1c** as a colorless oil, which crystallizes at 4 °C (2.9 g, 9.9 mmol, > 95%+).§ Spectral and physical data were in accordance with the literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 2.26 (s, 3H), 1.95 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 127.3, 115.4, 84.1, 24.9, 24.7, 12.0, 9.8. ^{11}B NMR (96 MHz, $CDCl_3$) δ 27.1, 22.5§. §Contaminated with pinBOH.[7] +Yield based on B_2pin_2.

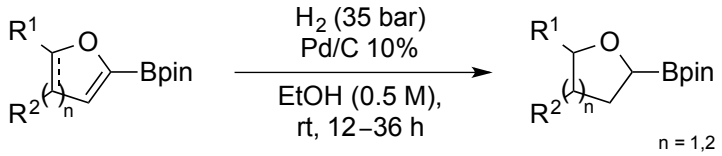
***tert*-Butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl)methoxy)silane (1e)**



$C_{17}H_{31}BO_4Si$
MW: 338.21

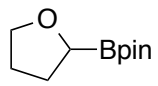
From **a1e** (1.73 g, 8.0 mmol) following **GP1**. The crude residue was purified by Kugelrohr distillation (158 – 161 °C, 2.4 mbar) to afford **1e** as a colorless oil (1.2 g, 3.56 mmol, 90%+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 3.3 Hz, 1H), 6.30 (d, J = 3.3 Hz, 1H), 4.72 (s, 2H), 1.34 (s, 12H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.1, 124.4, 107.4, 84.1, 58.9, 25.9, 24.7, 18.4, -5.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 27.2, 22.5§. IR (neat): 2929, 2857, 1538, 1371, 1341, 1254, 1144, 1106, 1076, 833, 776, 691 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{31}O_4BSiNa$ $[M+Na]^+$: 361,1977; found: 361,1974. §Contaminated with pinBOH.[9] +Yield based on B_2pin_2.

2.5 General Procedure 2 (GP2): Palladium-catalyzed hydrogenation to furnish 2a–e



To a beaker equipped with a crosshead magnetic stirring bar was added the 1-alkoxy boronic acid pinacol esters **2a–e** (1.0 equiv), 10% Pd/C and EtOH (0.5 M) under a stream of N_2 atm. The reaction mixture was placed in an autoclave which was purged once with H_2 (10 bar) and then filled with H_2 (35 bar). After being stirred at rt for 12–36 h, the hydrogen was carefully released. The reaction mixture was then filtered over a pad of celite (washed with TBME) and the volatiles were removed *in vacuo*.

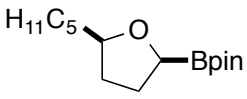
4,4,5,5-Tetramethyl-2-tetrahydrofuran-2-yl-1,3,2-dioxaborolane (2a)



$C_{10}H_{19}BO_3$
MW: 198.14

From 2-(2-Furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.04 g, 10.0 mmol) following **GP2**, to afford **2a** as a colorless oil (1.9 g, 9.7 mmol, 97%). Spectral and physical data were in accordance with the literature.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (q, *J* = 6.9 Hz, 1H), 3.63 (q, *J* = 7.6 Hz, 1H), 3.42 (dd, *J* = 10.7, 7.2 Hz, 1H), 2.14 – 1.98 (m, 1H), 1.95 – 1.79 (m, 2H), 1.78 – 1.63 (m, 1H), 1.28 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.9, 69.1, 28.2, 26.3, 24.8[§], 24.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.5, 22.3[§]. [§]Contaminated with pinBOH.[7]

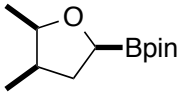
4,4,5,5-Tetramethyl-2-(5-pentyltetrahydrofuran-2-yl)-1,3,2-dioxaborolane (2b)



11:1 dr
$C_{15}H_{29}BO_3$
MW: 268.22

From **1b** (1.8 g, 7.0 mmol) following **GP2**, to afford **2b** as a mixture of diastereomers in a 11:1 ratio*, as a colorless oil (1.2 g, 4.5 mmol, 64%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 – 3.64 (m, 1H), 3.48 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.82 – 1.67 (m, 2H), 1.48 – 1.36 (m, 2H), 1.27 (s, 18H), 0.89 (app t, *J* = 6.9 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.8, 81.3, 35.4, 32.0, 31.6, 27.9, 26.1, 24.8[§], 24.7, 22.6, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.4, 22.3[§]. IR (neat): 2929, 2858, 1371, 1331, 1143, 1050, 970, 849, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{29}O_3BNa$ $[M+Na]^+$: 291.2102; found: 291.2108. *Determined by GC analysis on the crude residue. [§]Contaminated with pinBOH.[7]

2-(4,5-Dimethyltetrahydrofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)

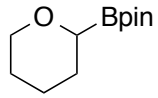


$C_{12}H_{23}BO_3$
MW: 226.17

From **1c** (750 mg, 3.4 mmol) following **GP2**, to afford **2c** as a single diastereomer as a colorless oil (362 mg, 1.6 mmol, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (p, *J* = 6.4 Hz, 1H), 3.53 (dd, *J* = 10.1, 8.0 Hz, 1H), 2.34 – 2.16 (m, 2H), 1.44 (dt, *J* = 10.2, 5.4 Hz, 1H), 1.27 (s, 12H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ

83.8, 78.6, 36.8, 36.6, 24.7, 16.1, 15.2. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.5. IR (neat): 2974, 1371, 1332, 1143, 950, 854, 668 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{23}O_3BNa$ $[M+Na]^+$: 249.1632; found: 249.1631.

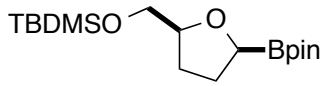
4,4,5,5-Tetramethyl-2-(tetrahydro-2*H*-pyran-2-yl)-1,3,2-dioxaborolane (2d)



$C_{11}H_{21}BO_3$
MW: 212.16

From 3,4-Dihydro-2*H*-pyran-6-boronic acid pinacol ester (1.54 g, 7.3 mmol) following **GP2**, to afford **2d** as a colorless oil (1.4 g, 6.7 mmol, 92%). Spectral and physical data were in accordance with the literature.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 – 3.99 (m, 1H), 3.40 (td, *J* = 11.7, 2.4 Hz, 1H), 3.35 – 3.29 (m, 1H), 1.90 – 1.79 (m, 1H), 1.71 – 1.57 (m, 3H), 1.55 – 1.43 (m, 2H), 1.27 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.9, 69.7, 28.0, 26.4, 24.8[§], 24.7, 24.4. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.1, 22.2[§]. [§]Contaminated with pinBOH.[7]

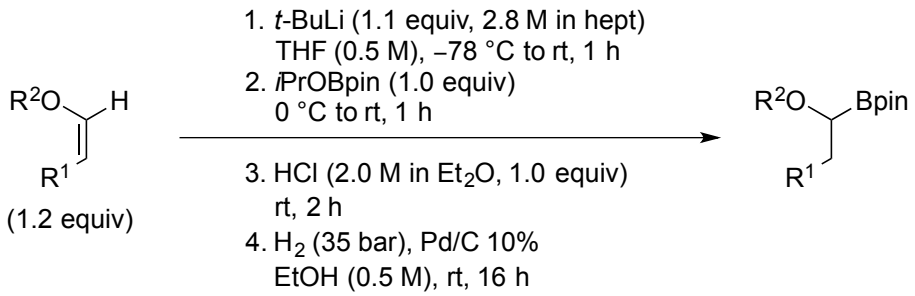
***tert*-Butyldimethyl(((2*S*,5*S*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)tetrahydro-furan-2-yl)methoxy)silane (2e)**



9:1 dr
$C_{17}H_{35}BO_4Si$
MW: 342.24

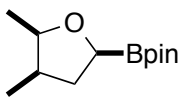
From **1e** (1.0 g, 3.0 mmol) following **GP2**, to afford **2e** as a mixture of diastereomers in a 9:1 ratio*, as a colorless oil (917 mg, 2.7 mmol, 89%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 – 3.85 (m, 1H), 3.73 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.57 – 3.39 (m, 2H), 1.97 (ddt, *J* = 11.6, 8.3, 6.1 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.26 (s, 12H), 0.89 (s, 9H), 0.05 (s, 6H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.8, 80.5, 65.7, 29.1, 27.8, 26.0, 24.74, 24.71, 18.4, -5.2, -5.3. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.4, 22.1[§]. IR (neat): 2928, 2856, 1472, 1371, 1334, 1252, 1142, 1069, 1006, 971, 831, 775, 672 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{36}O_4BSi$ $[M+H]^+$: 343.2470; found: 343.2457. *Determined by GC analysis on the crude residue. [§]Contaminated with pinBOH.[9]

2.6 General Procedure 3 (GP3): Borylation/Hydrogenation sequence with *i*PrOBpin to furnish 2c and 2j



A one-neck, round-bottom flask was charged with the corresponding enol ether (1.2 equiv) and THF (0.5 M) and the resulting solution was cooled down to –78 °C. A solution of *tert*-butyllithium (2.8 M in heptanes, 1.1 equiv) was added dropwise at this temperature, then the cooling bath was removed and the contents were stirred at rt for 1 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv) was then added at 0 °C and the reaction mixture was warmed up to rt and stirred for 1 h. A dry solution of HCl (1.0 equiv, 2.0 M in Et_2O) was added at rt and the reaction mixture was left to stir until the turbid solution turned clear (2–3 h). The contents were then partitioned with TBME (50 mL) and water (50 mL) and the two phases were separated. The aqueous phase was back-extracted with TBME (2×10 mL), and the collected ethereal phases were washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. To a beaker equipped with a crosshead magnetic stirring bar was successively added the crude residue, 10% Pd/C and EtOH (0.5 M) under a stream of N_2 atm. The reaction mixture was placed in an autoclave which was purged once with H_2 (10 bar) and then filled with H_2 (35 bar). After being stirred at rt for 16 h, the hydrogen was carefully released. The reaction mixture was filtered over a pad of celite (washed with TBME) and the volatiles were removed *in vacuo*.

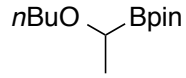
2-(4,5-Dimethyltetrahydrofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)



$C_{12}H_{23}BO_3$
MW: 226.17

From **1c** (2.56 mL, 24.0 mmol) following **GP3**, to afford **2c** as a colorless oil (3.8 g, 16.8 mmol, 83%). See above for spectral and physical data.

2-(1-Butoxyethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2j)



$C_{12}H_{25}BO_3$
MW: 228.19

From *n*-butyl vinyl ether (4.65 mL, 36.0 mmol) following **GP3**. The crude residue was purified by vacuum distillation (89 – 81 °C head, 2.4 mbar) to afford **2j** as a colorless oil (3.38 g, 14.8 mmol, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 – 3.35 (m, 2H), 3.30 (q, J = 7.5 Hz, 1H), 1.63 – 1.48 (m, 2H),

1.42 – 1.32 (m, 2H), 1.28 – 1.24 (m, 15H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.8, 70.0, 32.2, 25.0, 24.7, 19.5, 16.5, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.6. IR (neat): 2960, 2933, 2871, 1371, 1330, 1225, 1143, 1105, 965, 669 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{25}O_3BNa$ $[M+Na]^+$: 251.1789; found: 251.1792.

2.7 Synthesis of DTBHN and MeOBcat

Di-*tert*-butyl hyponitrite (DTBHN)

t-BuON=NO*t*-Bu
$C_8H_{18}N_2O_2$
MW: 174.24

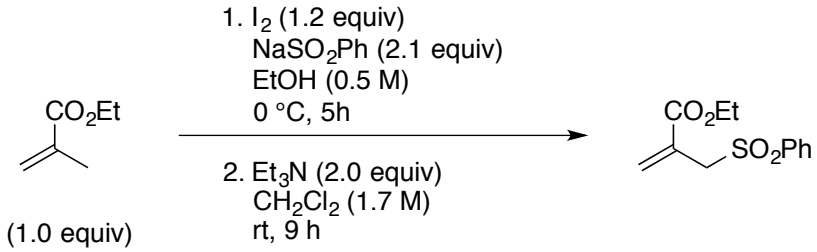
DTBHN was prepared according to a slightly altered literature procedure.[13] In a 250 mL three-necks flask equipped with a stirring bar was loaded sodium *trans*-hyponitrite hydrate (8.15 g) which was then dried to constant weight (5.58 g, 45.0 mmol, 1.0 equiv). In another flask, $ZnCl_2$ hydrate (14 g) was melted under stirring *in vacuo* (thrice) in order to dry it. From the resulting block of grey solid, pieces with a total weight of 8.6 g (63.1 mmol, 1.2 equiv) were (quickly) transferred into a two-neck flask, dried another 10 min under vacuum, and then suspended in Et_2O (35.0 mL) first with stirring for 2 h then with sonication for another 20 min until no more pieces of $ZnCl_2$ were visible. To the dry hyponitrite was added Et_2O (30.0 mL) and *tert*-butylbromide (47.0 mL, 418 mmol, 8.0 equiv) and the resulting milky white mixture was cooled to –10 °C (internal temperature) using an ice/NaCl/water bath. Then, the $ZnCl_2$ suspension was transferred into the reaction vessel with the hyponitrite using a cannula (Ø = 1 mm) at a rate that the internal temperature did not exceed –5 °C. After complete addition, the mixture was allowed to reach rt and stirred for another 1.5 h at this temperature. The reaction mixture was filtered and the remaining solid was washed with Et_2O (3×10 mL). The resulting yellow solution was transferred into a separatory funnel and water was added. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with aq. sat. NaCl, dried over Na_2SO_4 and the volatiles were removed under reduced pressure (bath temperature 20 °C, 400 mbar, end to 50 mbar for a short time). The obtained solid was crystallized from *n*-pentane to furnish almost colorless crystals in three crops (all crops were washed with cold pentane). Recrystallization from *n*-pentane of the combined crops furnished the product as colorless, transparent crystals (3.43 g, 19.8 mmol, 37%). DTBHN was stored for months at 4 °C. Spectral and physical data were in accordance with the literature.[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.2, 27.8.

2-Methoxybenzo[*d*][1,3,2]dioxaborole (MeOBcat)

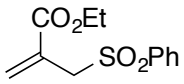
MeOBcat
$C_7H_7BO_3$
MW: 150.05

A one-neck, 100 mL round-bottom flask was charged with catecholborane (4.0 mL, 37.5 mmol, 1.0 equiv) and benzene (25.0 mL, 1.5 M). MeOH (1.52 mL, 37.5 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred at rt until no more H_2 evolution was visible (ca. 1 h). The volatiles were removed *in vacuo* and the residue was purified by vacuum distillation (43–45 °C head, 4×10^{-2} mbar) to afford **MeOBcat** as a colorless oil (3.2 g, 21.1 mmol, 57%). Spectral and physical data were in accordance with the literature.[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.59 (m, 2H), 6.48 – 6.42 (m, 2H), 3.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 121.1, 110.8, 51.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 23.4.

2.8 Synthesis of the radical trap 7



Ethyl 2-(benzenesulfonylmethyl)prop-2-enoate (7)



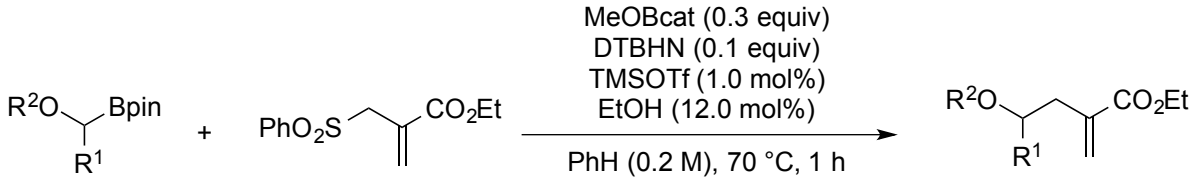
$C_{12}H_{14}O_4S$
MW: 254.06

A three-necks, 250 mL round-bottom flask was charged with 2-(ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone (7.4 mL, 60.0 mmol, 1.0 equiv) and ethanol (120 mL, 0.5 M). The contents were cooled to 0 °C and iodine (18.3 g, 72.0 mmol, 1.2 equiv) and benzenesulfinic acid sodium salt (20.7 g, 126 mmol, 2.1 equiv) were added in sequence. The reaction mixture was stirred at 0 °C for 5 h, then diluted with CH_2Cl_2 (100 mL) and the two phases were separated. The organic phase was washed with water (2×100 mL) and the combined aqueous phase was back-extracted with CH_2Cl_2 (2×25 mL). The collected organic phase was washed with sat. aq. $NaHCO_3$ (100 mL), 5% aq. $Na_2S_2O_4$ (2×100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To a solution of the crude residue in CH_2Cl_2 (35 mL, 1.7 M) was added Et_3N (16.7 mL, 120 mmol, 2.0 equiv) dropwise over a period of 10 min and the contents were stirred at rt for 9 h. The reaction mixture was concentrated *in vacuo* to about half of its original volume and the resulting

concentrate was purified by FCC on silica gel (cyclohexane/TBME 1:1) to afford **7** as a clear viscous oil (11.6 g, 45.6 mmol, 76%). Spectral data were in accordance with the literature.[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.68 – 7.61 (m, 1H), 7.58 – 7.50 (m, 2H), 6.51 (d, J = 0.6 Hz, 1H), 5.93 – 5.91 (m, 1H), 4.17 (d, J = 0.7 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 138.4, 133.9, 133.4, 129.2, 129.1, 128.8, 61.5, 57.5, 14.0.

3. General Experimental Procedures for the Deboronative Radical Chain Reactions

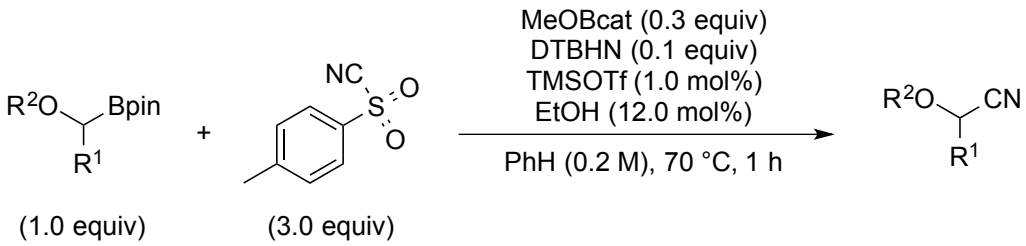
3.1 General Procedure 4 (GP4): Allylation of 2a–f and 2k–l with 7



(1.0 equiv) (1.5 equiv)

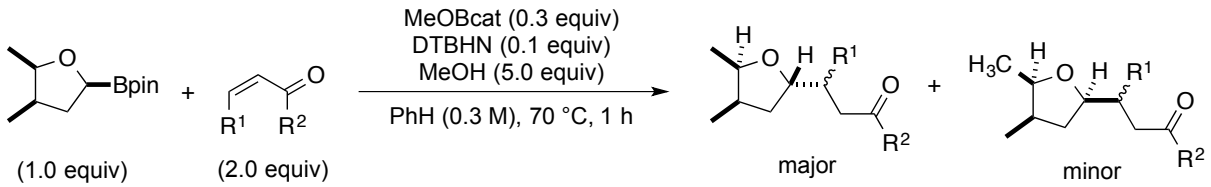
A two-necks, 25 mL round-bottom flask equipped with a condenser was charged with **2a–f**, **2k–l** (1.0 equiv), PhH (0.2 M), MeOBcat (0.3 equiv, 1.0 M in PhH), 2-((phenylsulfonyl) methyl)acrylate (1.5 equiv), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), EtOH (12.0 mol%) and DTBHN (0.1 equiv) under a stream of N_2 atm and the contents were heated at 70 °C for 1 h. The reaction mixture was cooled to rt and partitioned between TBME (10 mL) and water (10 mL). The phases were separated and the aqueous phase was back-extracted with TBME (2×5 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$ (20 mL), sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

3.2 General Procedure 5 (GP5): Cyanation of 2a–d and 2k with *p*-toluenesulfonyl cyanide



A two-necks, 25 mL round-bottom flask equipped with a condenser was charged with **2a–d**, **2k** (1.0 equiv), PhH (0.2 M), MeOBcat (0.3 equiv, 1.0 M in PhH), *p*-toluenesulfonyl cyanide (3.0 equiv), TMSOTf (1.0 mol%, 0.05 M in CH_2Cl_2), EtOH (12.0 mol%) and DTBHN (0.1 equiv) under a stream of N_2 atm and the contents were heated at 70 °C for 1 h. The contents were cooled down to rt and partitioned between TBME (10 mL) and water (10 mL). The phases were separated and the aqueous phase was back-extracted with TBME (2×5 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$ (20 mL), sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

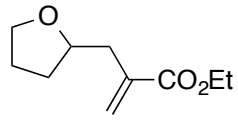
3.3 General Procedure 6 (GP6): Deboronative radical addition of 2c to Michael acceptors



A two-necks, 25 mL round-bottom flask equipped with a condenser was charged with **2c** (1.0 equiv), PhH (0.3 M), MeOBcat (0.3 equiv, 1.0 M in PhH), the corresponding enone (2.0 equiv), MeOH (5.0 equiv) and DTBHN (0.1 equiv) under a stream of N_2 atm and the contents were heated at 70 °C for 1 h, then partitioned at rt between TBME (10 mL) and 1 M aq. HCl (10 mL). The phases were separated and the aqueous phase was back-extracted with TBME (2×5 mL). The combined ethereal phases were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

4. Descriptions of Isolations and Characterizations of Deboronative Radical Chain Reaction Products

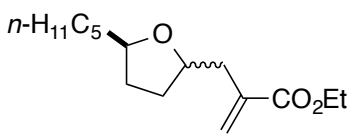
Ethyl 2-((tetrahydrofuran-2-yl)methyl)acrylate (3a)



$C_{10}H_{16}O_3$
MW: 184.11

From **2a** (198 mg, 1.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **3a** as a clear viscous oil (79 mg, 0.43 mmol, 43%). Spectral and physical data were in accordance with the literature.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, *J* = 1.5 Hz, 1H), 5.66 (d, *J* = 1.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.04 (p, *J* = 6.4 Hz, 1H), 3.87 (dt, *J* = 8.1, 7.0 Hz, 1H), 3.80 – 3.61 (m, 1H), 2.52 (dd, *J* = 6.5, 0.9 Hz, 2H), 2.12 – 1.76 (m, 3H), 1.61 – 1.43 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 137.9, 126.6, 77.6, 67.8, 60.7, 37.9, 31.2, 25.6, 14.2.

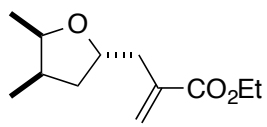
Ethyl 2-((5-pentyltetrahydrofuran-2-yl)methyl)acrylate (3b)



52:48 dr
$C_{15}H_{26}O_3$
MW: 254.19

From **2b** (268 mg, 1.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **3b** as a mixture of diastereomers in a 52:48 ratio*, as a clear viscous oil (191 mg, 0.75 mmol, 75%). *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.21 (d, *J* = 1.3 Hz, 1H *maj* + 1H *min*), 5.65 (d, *J* = 1.3 Hz, 1H *maj* + 1H *min*), 4.26 – 4.07 (m, 3H *major* + 2H *minor*), 4.07 – 3.89 (m, 1H *maj* + 1H *min*), 3.85 – 3.76 (m, 1H *min*), 2.64 – 2.35 (m, 2H *maj* + 2H *min*), 2.09 – 1.81 (m, 2H *maj* + 2H *min*), 1.65 – 1.21 (m, 13H *maj* + 13H *min*), 0.88 (app t, *J* = 6.6 Hz, 3H *maj* + 3H *min*). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 138.0, 137.9, 126.6, 126.5, 79.7, 78.8, 77.5, 77.0, 60.6, 38.3, 38.0, 36.2, 36.0, 32.0, 31.8, 31.7, 30.9, 30.8, 25.9, 22.7, 14.2, 14.1. IR (neat): 2929, 2853, 1758, 1714, 1449, 1183, 1149, 1034, 946 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{26}O_3Na$ $[M+Na]^+$: 277.1774; found: 277.1765. *Determined by GC analysis on the crude residue.

Ethyl 2-((4,5-dimethyltetrahydrofuran-2-yl)methyl)acrylate (3c)

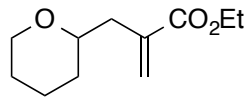


9:1 dr
$C_{12}H_{20}O_3$
MW: 212.14

From **2c** (678 mg, 3.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **3c** as a mixture of diastereomers in a 9:1 ratio*, as a clear viscous oil (422 mg, 2.0 mmol, 66%). *Major diastereomer* - ^{1}H NMR (300 MHz,

$CDCl_3$) δ 6.22 (d, *J* = 1.5 Hz, 1H), 5.64 (q, *J* = 1.2 Hz, 1H), 4.26 (p, *J* = 6.6 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.10 (qd, *J* = 6.4, 5.7 Hz, 1H), 2.60 – 2.37 (m, 2H), 2.28 – 2.19 (m, 1H), 1.85 – 1.69 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 137.8, 126.7, 76.9, 75.4, 60.7, 39.3, 38.9, 36.3, 16.0, 14.2, 14.1. IR (neat): 2965, 1713, 1456, 1377, 1322, 1147, 1093, 1027, 819 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{20}O_3Na$ $[M+Na]^+$: 235.1298; found: 235.1305. *Determined by GC analysis on the crude residue.

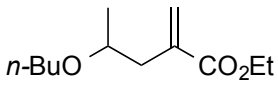
Ethyl 2-((tetrahydro-2H-pyran-2-yl)methyl)acrylate (3d)



$C_{11}H_{18}O_3$
MW: 198.13

From **2d** (212 mg, 1.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **3d** as a clear viscous oil (83 mg, 0.42 mmol, 42%).[§] Spectral and physical data were in accordance with the literature.[17] ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J* = 1.6 Hz, 1H), 5.63 (q, *J* = 1.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.93 (m, 1H), 3.53 – 3.32 (m, 2H), 2.54 – 2.36 (m, 2H), 1.88 – 1.72 (m, 1H), 1.66 – 1.44 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 137.4, 126.8, 76.1, 68.6, 60.6, 39.1, 31.8, 26.0, 23.5, 14.2. [§]Contaminated with *S*-phenyl benzenesulfonothiolate.[18]

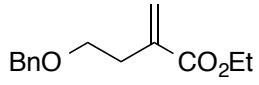
Ethyl 4-butoxy-2-methylenepentanoate (3j)



$C_{12}H_{22}O_3$
MW: 214.16

From **2j** (228 mg, 1.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **3j** as a clear viscous oil (174 mg, 0.81 mmol, 81%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (d, *J* = 1.5 Hz, 1H), 5.60 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.58 (sext, *J* = 6.3 Hz, 1H), 3.48 (dt, *J* = 9.2, 6.6 Hz, 1H), 3.37 (dt, *J* = 9.2, 6.6 Hz, 1H), 2.59 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.35 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.55 – 1.45 (m, 2H), 1.42 – 1.25 (m, 5H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 137.8, 126.7, 76.9, 75.4, 60.7, 39.3, 38.9, 36.3, 16.0, 14.2, 14.1. IR (neat): 2960, 2871, 1714, 1457, 1369, 1325, 1158, 1093, 1025, 942, 817 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{22}O_3Na$ $[M+Na]^+$: 237.1466; found: 237.1461.

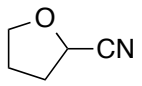
Ethyl 4-(benzyloxy)-2-methylenebutanoate (3k)



$C_{14}H_{18}O_3$
MW: 234.13

From **2k** (248 mg, 1.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 1:1) to afford **3k** as a colorless oil (153 mg, 0.65 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.13 (m, 5H), 6.22 (d, *J* = 1.4 Hz, 1H), 5.64 (d, *J* = 1.3 Hz, 1H), 4.51 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.72 – 2.50 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.5, 137.7, 128.5, 127.7, 127.7, 126.5, 72.9, 68.8, 60.8, 32.4, 14.3. IR (neat): 2981, 2857, 1712, 1365, 1300, 1151, 1095, 1026, 945, 817, 734, 696 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1329; found: 235.1326.

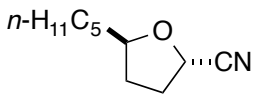
Tetrahydro-2H-pyran-2-carbonitrile (4a)



C_5H_7NO
MW: 97.05

From **2a** (79 mg, 0.4 mmol) following **GP5**. An internal standard (dodecane, 45 μL, 0.5 equivalent) was added along with substrates and reagents. After reaction, an aliquot was filtered through a pad of neutral aluminium oxide (ca. 1 cm in a Pasteur pipette and eluted with Et_2O). The resulting sample was injected in GC using the method described above.

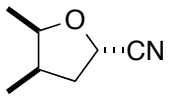
5-Pentyltetrahydrofuran-2-carbonitrile (4b)



57:43 dr
$C_{10}H_{17}NO$
MW: 167.13

From **2b** (268 mg, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **4b** as a mixture of diastereomers in a 57:43 ratio*, as a clear viscous oil (144 mg, 0.86 mmol, 86%). *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (dd, *J* = 7.5, 4.2 Hz, 1H *maj*), 4.64 (dd, *J* = 7.3, 3.7 Hz, 0.7H *min*), 4.18 – 4.03 (m, 1H *maj*), 4.00 (dd, *J* = 8.2, 5.9 Hz, 0.7H *min*), 2.36 – 2.09 (m, 3H *maj* + 2.1H *min*), 1.84 – 1.31 (m, 9H *maj* + 6.3H *min*), 0.92 – 0.88 (m, 3H *maj* + 2.1H *min*). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.1 (*min*), 119.8 (*maj*), 82.3 (*min*), 81.0 (*maj*), 66.2 (*maj*), 65.9 (*min*), 35.7 (*min*), 35.0 (*maj*), 32.3 (*min*), 31.9 (*maj*), 31.8 (*min*), 31.5 (*maj*), 31.0 (*min*), 30.3 (*maj*), 25.9 (*min*), 25.8 (*maj*), 22.7 (*maj* + *min*), 14.1 (*maj* + *min*). IR (neat): 2956, 2930, 1461, 1056 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{16}NO$ $[M-H]^+$: 166.1226; found: 166.1224. *Determined by GC analysis on the crude residue.

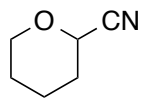
4,5-Dimethyltetrahydrofuran-2-carbonitrile (4c)



8:2 dr
$C_7H_{11}NO$
MW: 125.08

From **2c** (212 mg, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **4c** as a mixture of diastereomers in a 8:2 ratio*, as a clear viscous oil (106 mg, 0.85 mmol, 85%). *Mixture of diastereomers* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, *J* = 8.2, 4.3 Hz, 1H *maj*), 4.55 (dd, *J* = 8.5, 6.1 Hz, 0.4H *min*), 4.27 (p, *J* = 6.3 Hz, 1H *maj*), 4.14 (p, *J* = 6.4 Hz, 0.4H *min*), 2.53 – 2.37 (m, 2H *maj* + 0.4H *min*), 2.33 (hept, *J* = 6.9 Hz, 0.4H *min*), 2.06 – 1.96 (m, 1H *maj* + 0.4H *min*), 1.20 (d, *J* = 6.5 Hz, 1.3H *min*), 1.14 (d, *J* = 6.4 Hz, 3H *maj*), 1.06 (d, *J* = 7.0 Hz, 1.3H *min*), 0.95 (d, *J* = 6.9 Hz, 3H *maj*). *Mixture of diastereomers* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.3 (*min*), 120.1 (*maj*), 80.2 (*min*), 79.1 (*maj*), 65.0 (*maj*), 64.3 (*min*), 39.4 (*maj*), 39.0 (*min*), 36.6 (*min*), 35.6 (*maj*), 15.9 (*min*), 15.7 (*maj*), 14.01 (*maj*), 13.96 (*min*). IR (neat): 2972, 1454, 1382, 1338, 1087, 1050, 1008, 850 cm^{-1}. HRMS (ESI) calcd. for $C_7H_{11}NONa$ $[M+Na]^+$: 148.0729; found: 148.0733. *Determined by GC analysis on the crude residue.

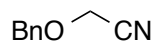
Tetrahydro-2*H*-pyran-2-carbonitrile (4d)



C_6H_9NO
MW: 111.07

From **2d** (212 mg, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 7:3) to afford **4d** as a mixture with $TolSO_2STol$[§] in a 1:2 ^{1}H NMR ratio, as a clear oil (44 mg, 0.4 mmol, 40%).[19,20] Spectral and physical data were in accordance with the literature.[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 1.70 (m, 1H)[§], 7.27 – 7.13 (m, 3H)[§], 4.63 (t, *J* = 4.4 Hz, 1H), 3.89 (dt, *J* = 12.2, 6.2 Hz, 1H), 3.76 (dt, *J* = 11.9, 4.6 Hz, 1H), 1.99 – 1.70 (m, 4H), 1.67 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.9, 66.2, 65.1, 29.2, 25.0, 20.2.

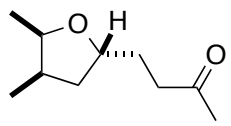
2-(Benzyloxy)acetonitrile (4k)



C_9H_9NO
MW: 147.07

From **2k** (248 mg, 1.0 mmol) following **GP5**. The crude residue was purified by FCC on silica gel with a short pad of neutral aluminium oxide at the top of the column (*n*-pentane/CH_2Cl_2 7:3) to afford **4k** as a colorless oil (138 mg, 0.94 mmol, 94%). Spectral and physical data were in accordance with the literature.[22,23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 4.65 (s, 2H), 4.23 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 128.8, 128.7, 128.4, 115.9, 73.1, 54.8.

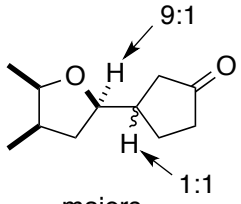
4-(4,5-Dimethyltetrahydrofuran-2-yl)butan-2-one (5c)



8:2 dr
$C_{10}H_{18}O_2$
MW: 170.13

From **2c** (212 mg, 1.0 mmol) and but-3-en-2-one (160 µL, 2.0 mmol) following **GP6**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **5c** as a mixture of *trans/cis* diastereomers in a 8:2 ratio*, as a yellow oil (163 mg, 0.96 mmol, 96%). *Mixture of diastereomers* - ^{1}H NMR (400 MHz, C_6D_6) δ 3.95 – 3.87 (m, 2H), 3.82 (p, *J* = 6.5 Hz, 0.3H), 3.62 (tdd, *J* = 8.5, 6.6, 4.3 Hz, 0.3H), 2.30 (app t, *J* = 7.0 Hz, 0.4H), 2.26 (app t, *J* = 7.1 Hz, 1H), 2.18 (app t, *J* = 7.5 Hz, 1H), 2.14 (app t, *J* = 7.5 Hz, 0.4H), 1.93 – 1.72 (m, 2H), 1.68 (s, 3.4H), 1.67 – 1.62 (m, 2.5H), 1.43 – 1.39 (m, 2.7H), 1.01 (d, *J* = 6.4 Hz, 0.8H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.93 – 0.87 (m, 0.3H), 0.73 (d, *J* = 7.0 Hz, 0.8H), 0.71 (d, *J* = 7.0 Hz, 3H). *Mixture of diastereomers* - ^{13}C NMR (101 MHz, C_6D_6) δ 206.3 (*maj*), 206.2 (*min*), 77.4 (*min*), 77.2 (*min*), 76.6 (*maj*), 76.0 (*maj*), 40.44 (*min*), 40.35 (*maj*), 40.3 (*min*), 40.0 (*maj*), 36.8 (*maj*), 36.5 (*min*), 31.2 (*maj*), 31.1 (*min*), 29.5 (*maj*), 29.4 (*min*), 16.9 (*min*), 16.2 (*maj*), 15.5 (*min*), 14.2 (*maj*). IR (neat): 2966, 2931, 2872, 1715, 1358, 1162, 1094cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1380; found: 171.1373. *Determined by GC analysis on the crude residue.

3-(4,5-Dimethyltetrahydrofuran-2-yl)cyclopentan-1-one (6c)



majors
$C_{11}H_{18}O_2$
MW: 182.13

From **2c** (212 mg, 1.0 mmol) and cyclopent-2-en-1-one (168 µL, 2.0 mmol) following **GP6**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **6c** as a mixture of diastereomers in a 9:9:1:1 ratio*, as a colorless oil (171 mg, 0.94 mmol, 94%). *Majors diastereomers* - ^{1}H NMR (300 MHz, CD_2Cl_2) δ 4.10 – 4.00 (m, 2H), 3.99 – 3.91 (m, 2H), 2.43 – 2.13 (m, 10H), 2.10 – 1.56 (m, 10H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 6H). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, CD_2Cl_2) δ 219.3 (*maj*), 219.09 (*min*), 219.08 (*maj*), 82.1 (*min*), 81.8 (*min*), 80.4 (*maj*), 80.1 (*maj*), 78.1 (*maj*), 77.9 (*maj*), 77.8 (2x *min*), 43.3 (*maj*), 43.2 (*maj*), 43.1 (*min*), 42.9 (*min*), 42.4 (*min*), 42.3 (*min*), 42.2 (*maj*), 42.1 (*maj*), 38.74, 38.69, 38.67, 38.66, 37.30 (*maj*), 37.25 (*maj*), 36.8 (*min*), 36.7 (*min*), 26.74 (*min*), 26.71 (*min*), 26.54 (*maj*), 26.45 (*maj*), 17.2 (*min*), 17.1 (*min*), 16.32 (*maj*), 16.31 (*maj*), 15.5 (*min*), 15.4 (*min*), 14.4 (2x *maj*). IR (neat): 2964, 2932, 2874, 1738, 1458, 1405, 1378, 1157, 1093, 1003, 905, 731 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1380; found: 183.1375. *Determined by GC analysis on the crude residue.

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5

A General Approach for the Generation of 1-Alkoxyalkyl Radicals

Unpublished Results

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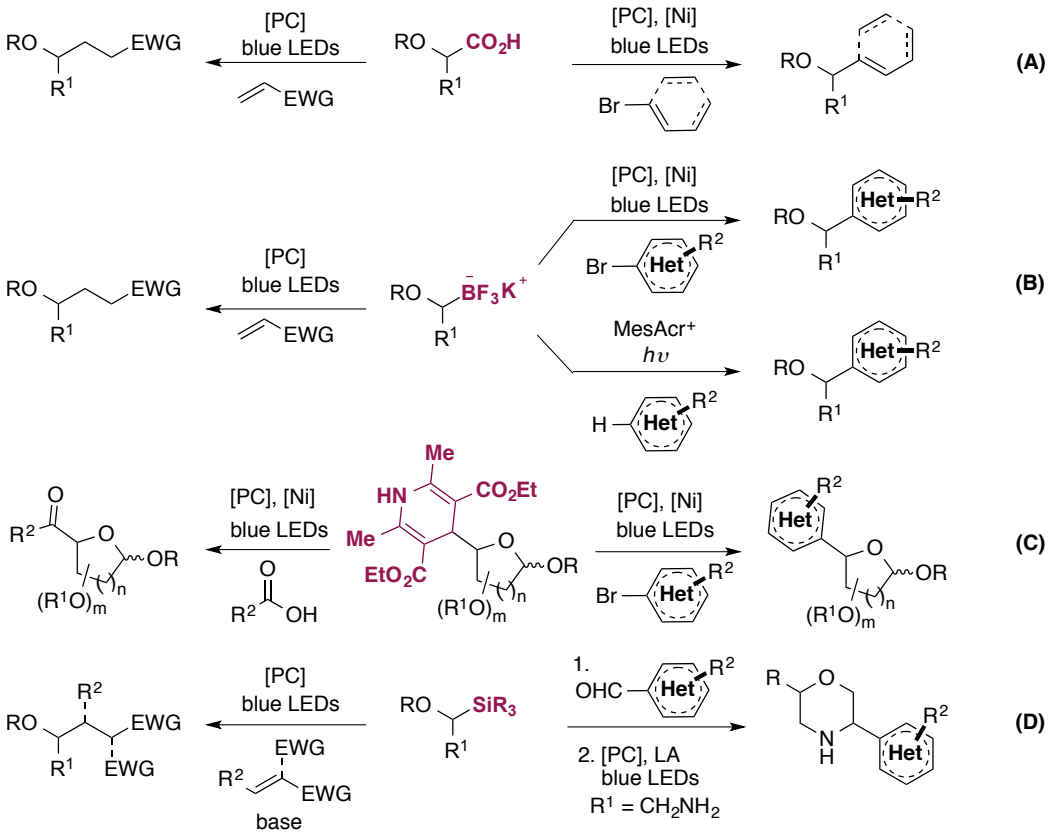
5. A general approach for the generation of 1-alkoxyalkyl radicals

5.1 Introduction

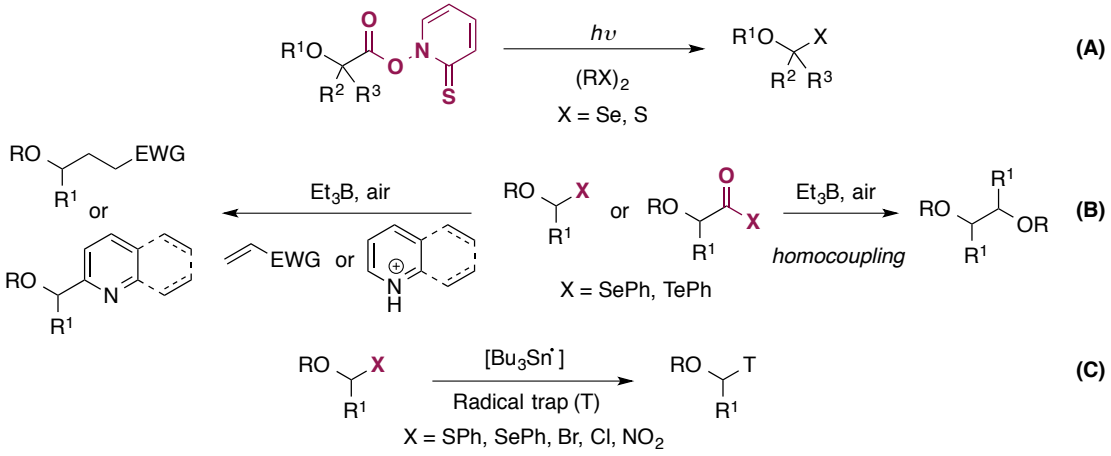
Over the last decade, the generation of 1-alkoxyalkyl radicals has emerged as a powerful strategy for the functionalization of cyclic and acyclic ethers. For example, the generation of 1-alkoxyalkyl radicals by oxidative processes has been well established. Strategies employing carbohydrate systems with hypervalent iodine (III) reagents have been reported.[1,2] Recently, the development of traceless activation groups (TAGs), such as carboxylates, have been achieved via visible-light mediated photoredox catalysis for radical Michael additions,[3,4] and for C(sp^3)—C(sp^2) cross coupling reactions by merging photoredox and nickel catalysis (Scheme 1, **A**).[5,6,7]



Scheme 1. Generation of 1-alkoxyalkyl radicals through oxidative processes. [PC] = photocatalyst

Alternatively, Molander and coworkers reported the generation of alkoxymethyl radicals from potassium alkoxyalkyltrifluoroborates by means of a single electron transfer (SET) photoredox process (Scheme 1, **B**).[8,9,10,11,12,13] By the same pathway as the carboxylate derivatives, applications to radical conjugate addition and C(sp^3)—C(sp^2) cross-coupling reactions were accomplished. More recently, Molander and coworkers also described a photoredox/nickel dual catalytic system using 1,4-dihydropyridines (1,4-DHPs) as glycosyl-based radical precursors (Scheme 1, **C**).[14,15,16] α-Silyl ether derivatives have been also reported as suitable radical precursors for the oxidative generation of 1-alkoxyalkyl radicals via SET processes (Scheme 1, **D**).[17,18,19]

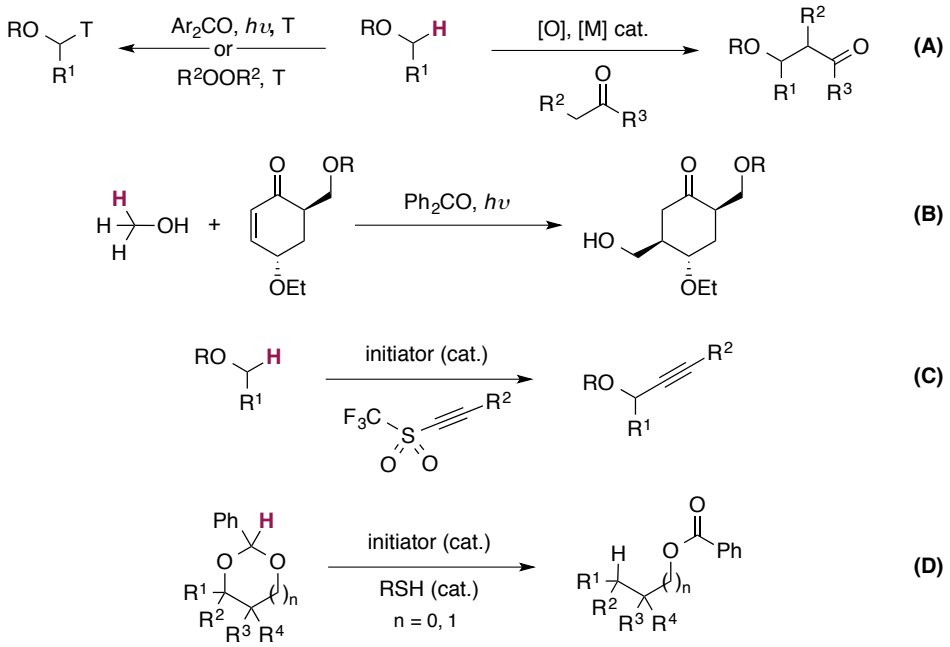
Access to mono-chalcogenide acetals (i.e., O,Se- or O,S-acetal) has been reported through the photochemically induced decarboxylation of Barton esters (Scheme 2, **A**).[20,21,22] Additionally, Inoue and coworkers developed a C—X abstraction method to generate 1-alkoxybridgehead radicals from the corresponding selenides or tellurides using a triethylborane (Et_3B)/air initiating system (Scheme 2, **B**).[21,22] They extended this methodology to the radical decarbonylation of 1-alkoxyacyl telluride and accomplished various multicomponent coupling reactions, as well as a radical-radical homocoupling approach for the synthesis of polyhydroxylated structures (Scheme 2, **B**).[23,24,25,26] Protocols involving tin-mediated radical chain reactions have also been well documented (Scheme 2, **C**)[27,28,29,30,31,32,33,34,35,36] although tin reagents are highly toxics, costly, and difficult to remove by conventional purification processes.[37]



Scheme 2. Generation of 1-alkoxyalkyl radicals via C—X abstraction. T = radical trap

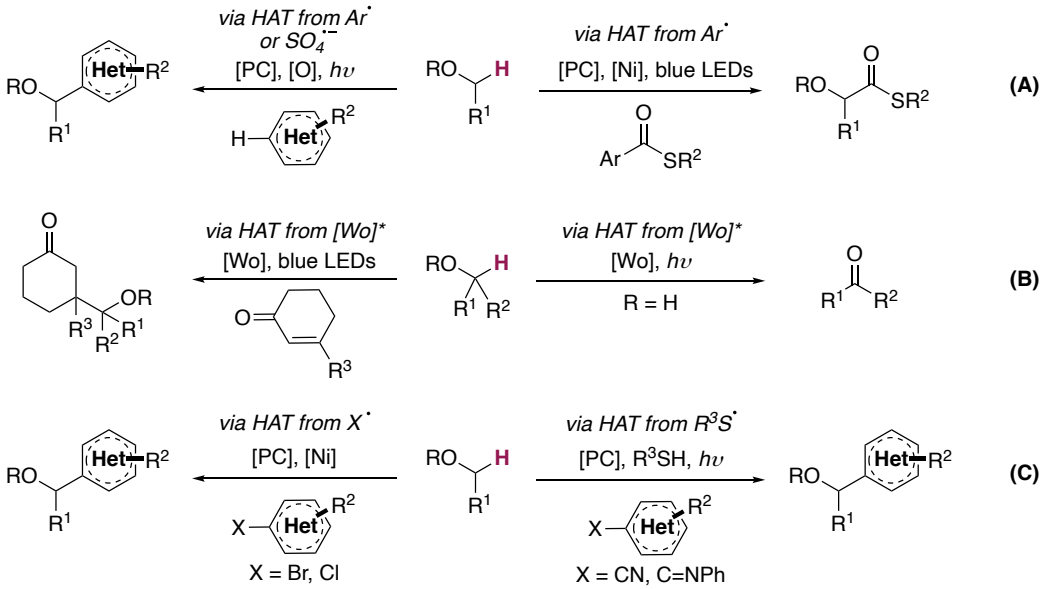
Alternatively, HAT from the C—H bond located adjacent to oxygen atoms has received much attention. A variety of approaches have emerged such as the oxidative cross coupling

between two different C—H bonds functionalization – *also known as cross dehydrogenative coupling (CDC) reaction* – which requires transition-metal catalysis and stoichiometric amount of oxidants (Scheme 3, **A**, right-hand side).[38,39] Other approaches involve the use of oxidants (commonly *tert*-butylhydroperoxide (TBHP), di-*tert*-butylperoxide (DTPB), and di-*tert*-butyl-hyponitrite (DTBHN)), photoexcited aryl ketones or electrophotocatalysis (Scheme 3, **A**, left-hand side).[38,39,40,41,42,43,44,45] For example, Fraser-reid and coworkers reported a benzophenone-initiated photoaddition of methanol to carbohydrate-derived α-enones to give the corresponding hydroxymethylated products (Scheme 3, **B**). However, these methodologies suffer from stoichiometric oxidants and high-energy light sources in most cases. In contrast, alkenylations of C—H bond located adjacent to oxygen atoms have been developed using substoichiometric amounts of radical initiators (i.e., AIBN or peroxide) (Scheme 3, **C**).[46,47,48,49,50] The reaction proceeds through the fragmentation of (trifluoromethyl)sulfonyl radicals, which in turn generates trifluoromethyl radicals thereby ensuring the propagation of the radical cascade. Similarly, Roberts and coworkers investigated the thiol-catalyzed redox rearrangement of some carbohydrate benzylidene acetals (Scheme 3, **D**).[51,52,53,54] The thiol operates as a protic polarity-reversal catalyst thereby ensuring efficient propagation of the radical-chain reaction.



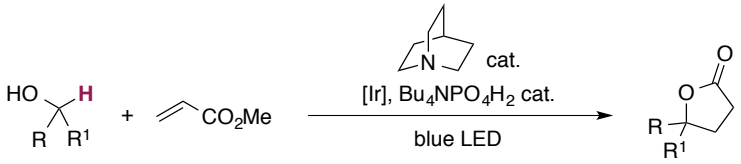
Scheme 3. Generation of 1-alkoxyalkyl radicals by HAT processes. (A) HAT by alkoxyl radicals (T = radical trap). (B) Benzophenone-initiated photoaddition of methanol to carbohydrate derivatives. (C) HAT by trifluoromethyl radicals. (D) HAT by thiyl radicals

In recent years, the direct functionalization of ethers has been accomplished via visible-light photoredox catalysis (Scheme 4, **A**).[55,56,57,58] Polyoxometalates such as the decatungstate anion $[W_{10}O_{32}]^{4-}$ have been exploited as photocatalysts for the activation of C—H bonds located adjacent to oxygen atoms, with applications to C—C bond formation and alcohol oxidations (Scheme 4, **B**).[59,60,61]



Scheme 4. Generation of 1-alkoxyalkyl radicals by merging SET and HAT processes. (A) HAT from in situ generated aromatic radicals. (B) HAT from photoexcited decatungstate (TBADT). (C) HAT from in situ generated thiyl or halogen radicals

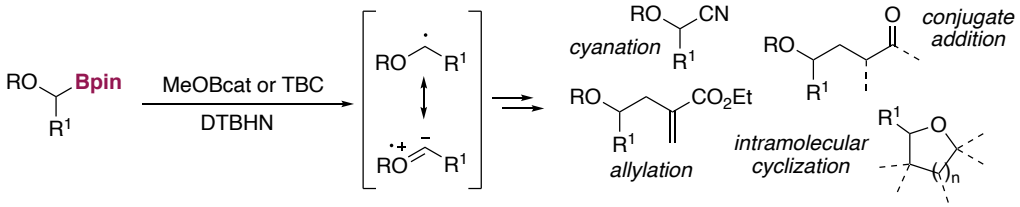
In contrast to the formation of α-amino radicals, the photoredox activation of ethers remains challenging because of their relatively much higher oxidation potentials ($E_{1/2}^{ox}$ > +2.4 V vs SCE for THF, THP, and Et_2O; *vs* $E_{1/2}^{ox}$ = +0.78 V vs SCE in MeCN for NEt_3).[62] This difficulty has been recently circumvented by merging photoredox catalysis with hydrogen atom transfer (HAT) reagents such as thiols[63,64,65] and halogen radicals generated *in situ* (Scheme 4, **C**).[66,67,66,68] In addition, Macmillan and coworkers investigated a photoredox protocol which involves transient quinuclidinium radicals generated *in situ* as HAT catalysts in combination with α-activation of alcohol C—H bonds with a hydrogen-bonding catalyst (Scheme 5).[69]



Scheme 5. Generation of 1-alkoxyalkyl radicals using quinuclidine as HAT catalyst

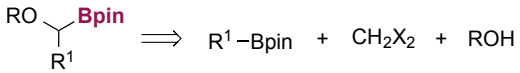
Although a variety of strategies have been developed for the generation of 1-alkoxyalkyl radicals, each method exhibits some inherent limitations (e.g., excess of ethers required, expensive catalysts, stoichiometric oxidants).

Our long-standing interest for the generation of radicals from organoboron species[70,71,72,73,74,75,76,77] prompted us to investigate the generation of 1-alkoxyalkyl radicals from readily available pinacol boronic ester precursors (R–Bpin) (Scheme 6). Organoboron derivatives have proven over the years to be an efficient source of alkyl radicals.[70,71,72,73] A few years ago, we demonstrated that highly reactive *B*-alkylcatecholboranes (R–Bcat) could be used as radical precursors for a wide range of transformations. However, the generation of radicals from the radical inactive R–Bpin is more attractive due its greater stability. In an earlier report, we have shown that the radical protodeboronation of R–Bpin was easily achievable via an *in situ* boron-transesterification with 4-*tert*-butylcatechol (TBC) catalyzed by sulfuric acid.[77] Recently we reported milder conditions for this transformation, and were able to broaden the scope of the method to include the formation of C—C and C—X bonds by employing substoichiometric quantities of catechol methyl borate (MeO–Bcat).[78] With this in mind, we questioned whether a stable and easy to handle R–Bpin could be used as a radical precursor for the generation of 1-alkoxyalkyl radicals.



Scheme 6. Conceptual framework for the generation of 1-alkoxyalkyl radicals by way of a nucleohomolytic substitution at boron

To the best of our knowledge, the formation of 1-alkoxyalkyl radicals from organoboron species by nucleohomolytic substitution at boron has not been described yet. Following our investigations on the preparation of 2-alkylated tetrahydrofurans and tetrahydropyrans via a radical deboronative pathway (see Chapter 4), we report herein a general protocol for the generation of 1-alkoxyalkyl radicals from 1-alkoxyalkyl pinacol boronic ester precursors, readily prepared from commercially available boronic esters by a Matteson homologation followed by a 1,2-metalate shift with diverse lithium alcoholates (Scheme 7).[79,80,81]



Scheme 7. Strategy for the preparation of 1-alkoxyalkyl pinacol boronic esters

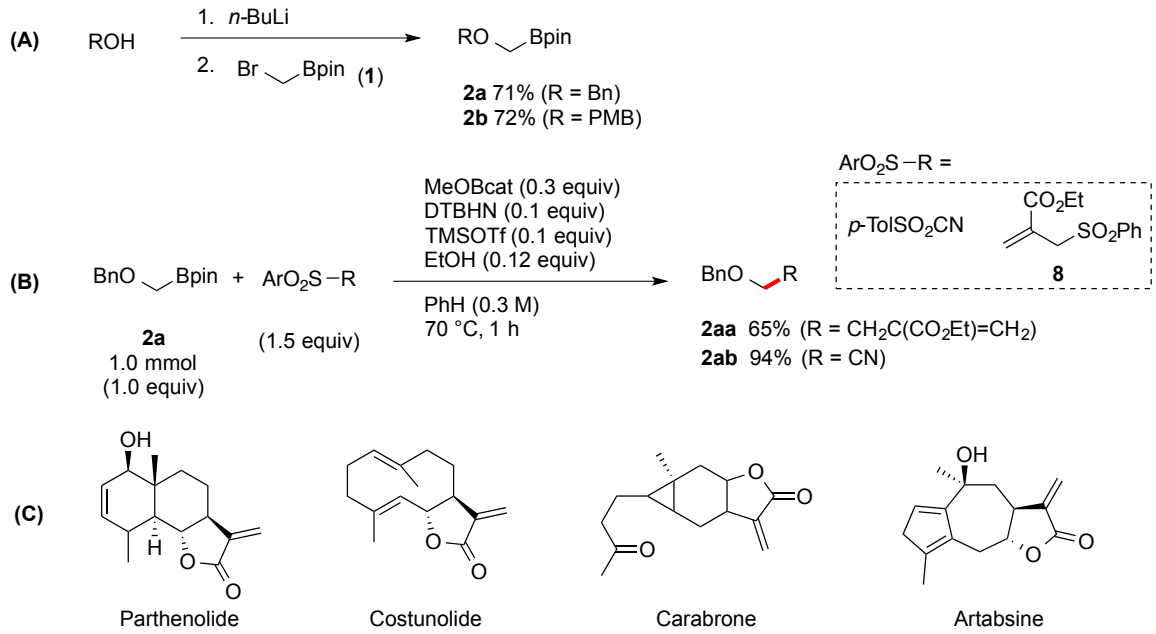
5.2 Results and discussion

5.2.1 Hydroalkoxymethylation of enones

5.2.1.a Preliminary results

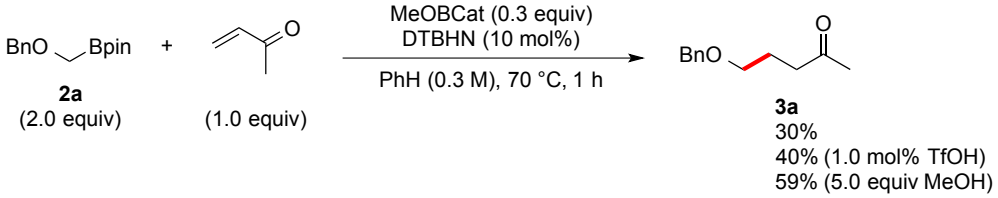
We have previously investigated the generation of 1-alkoxyalkyl radicals from cyclic ethers and their reactivity in C—C bond formations using sulfone-based radical traps (see Chapter 4). These results stimulated us to investigate further the reactivity of alkoxymethyl radicals using 1-alkoxymethyl pinacol boronic esters as radical precursors.

The synthesis of the radical precursors was readily performed starting from commercially available (bromomethyl)boronic acid pinacol ester **1**. This starting material can also be easily prepared by treatment of isopropoxy pinacol borate (*i*PrO–Bpin) with $LiCH_2Br$, followed by hydrolysis with dry HCl.[82] Next, **1** was reacted with a lithium alcoholate to yield **2a** and **2b** through a classical 1,2-metalate rearrangement (Scheme 8, **A**). The insertion of different protecting groups such as benzyl (Bn) and *p*-methoxybenzyl (PMB) will enable a broader choice of deprotection strategies to access hydroxymethylated substrates at the end of the overall sequence. Next, the suitability of **2a** to generate radicals was demonstrated using sulfone-based radical traps (see Chapter 4, compound **3k** and **4k**) and the corresponding allylated and cyanated products **2aa** and **2ab** were obtained in 65% and 94% yield, respectively (Scheme 8, **B**). The synthetic utility of this compounds has not been explored yet, although compounds of type **2aa** can be regarded as precursors of α-methylene-γ-lactone, an important core structure present in many natural and bioactive compounds (Scheme 8, **C**).[83,84,85,86]



*Scheme 8. (A) Preparation of pinacol benzyloxy- and p-methoxybenzyloxy-methyl boronic esters **2a** and **2b**. (B) Proof of concept: intermolecular reactions with pinacol benzyloxymethyl boronic ester to furnish **2aa** and **2ab** (yields of isolated products). (C) Structures of natural or bioactive compounds bearing α-methylene-γ-lactones*

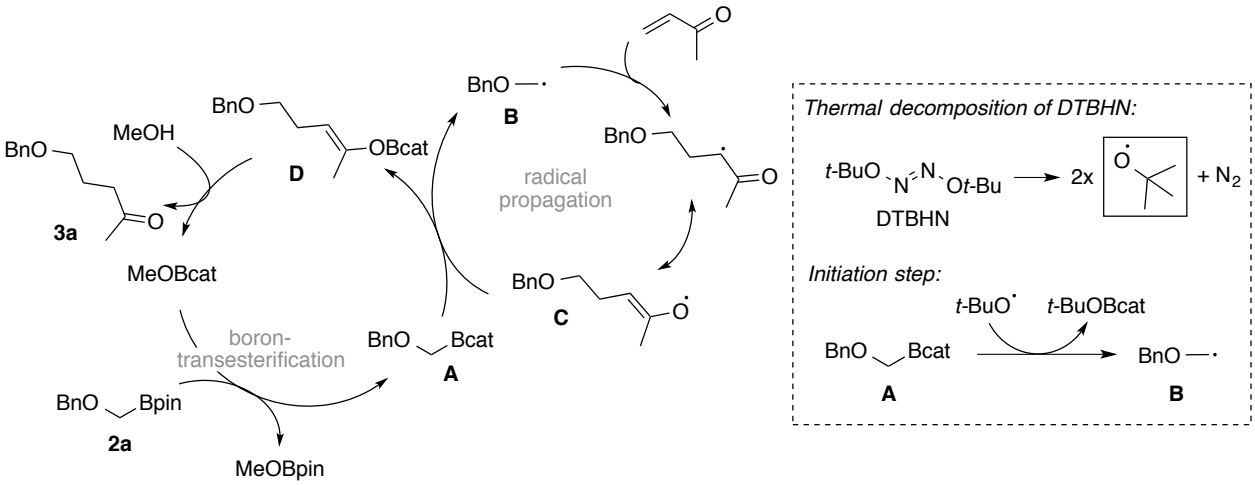
Inspired by the work of Fraser-Reid on the photochemical 1,4-addition of methanol to enones, we sought to develop an alternative radical deboronative approach for the conjugate addition of alkoxymethyl radical equivalents to enones.[87] Initial attempts to perform the 1,4-addition of radical precursor **2a** to 2-cyclopentenone in the absence of acid catalysis eventually provided **3a**, albeit in low yield (Scheme 9). Therefore, triflic acid catalyzed boron-transesterification of **2a** with catechol methyl borate (MeO–Bcat) was further examined and only a slight increase of the yield was observed. After a thorough screening of the reaction conditions (see Experimental Part), it turned out that the amount of MeOH was critical for the yield and the best result was obtained using five equivalents of MeOH.



Scheme 9. Conjugate addition to methyl vinyl ketone (^{1}H NMR yield)

A plausible reaction mechanism is provided in Scheme 10. The radical precursor **2a** is converted into the radical-active specie **A** by taking advantage of an *in situ* boron-

transesterification with MeO–Bcat. The 1-alkoxyalkyl radical **B** is generated in an initiation step from the reaction of **A** with *tert*-butoxyl radicals which are produced by the thermal decomposition of DTBHN (dashed frame). This radical then adds to the Michael acceptor to give an enolyl radical **C** which is trapped by the catechol boronic ester intermediate **A**, regenerating the benzyloxymethyl radical **B** in a chain process. The resulting boron-enolate **D** is then hydrolyzed with MeOH, providing the corresponding ketone **3a** and recycling the transesterifying species MeO–Bcat. In the absence of MeOH, evidence for the formation of an intermediate boron-enolate **D** is supported by the 30% yield observed for product formation (see Scheme 9), which corresponds to the amount of boron-enolate formed when no MeO–Bcat recycling process occurs. In other words, the role of MeOH is critical in the mechanism, and is reflected in a large boost for product yields. Yet, the exact role of MeOH in the transesterification process remains unclear.

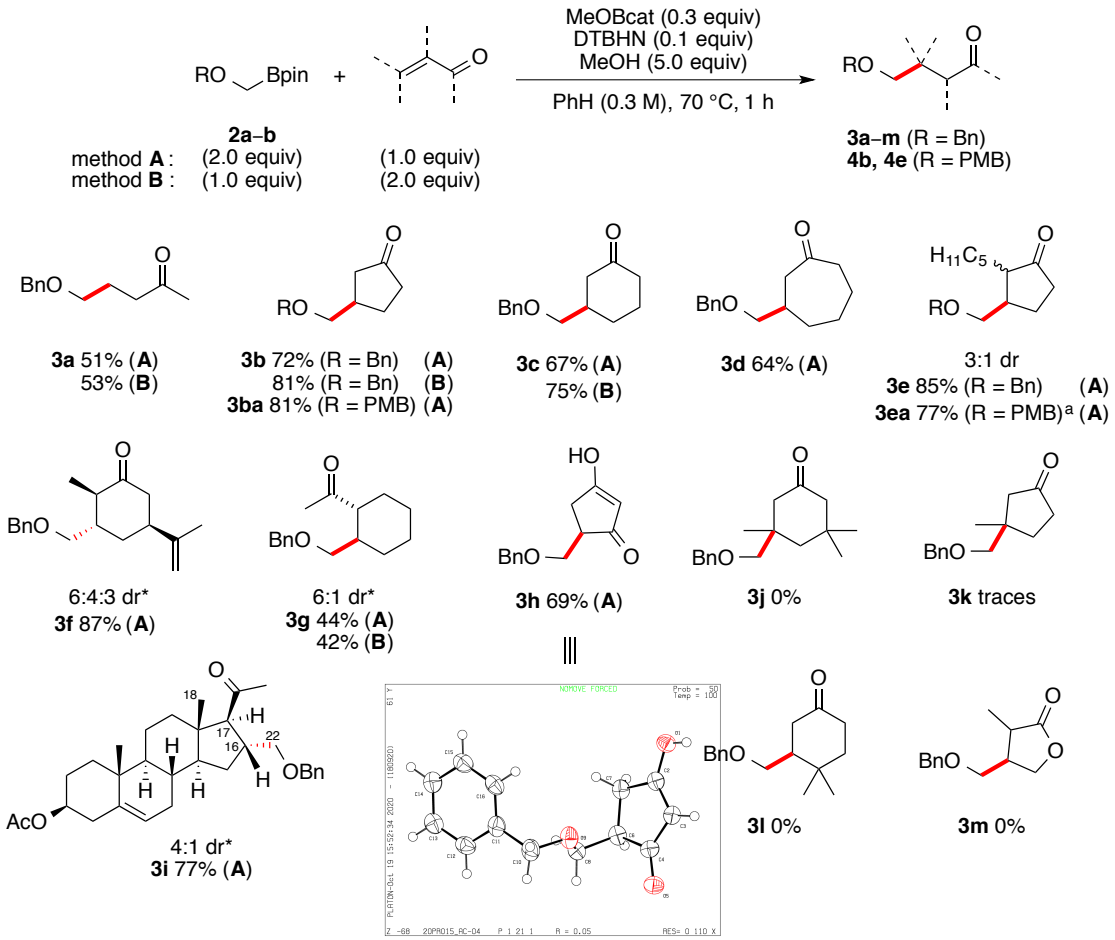


Scheme 10. Suggested mechanism for the deboronative radical chain conjugate addition to enones

5.2.1.b Scope of the reaction

Next, we explored the substrate scope of the 1,4-addition of 1-alkoxymethyl pinacol boronic esters **2a** and **2b** to electron-deficient alkenes (Scheme 11). Under the optimized conditions (i.e., using the enone as a limiting reagent and 2.0 equiv of radical precursors **2a–b**, method **A**), the reaction of **2a** with 2-cyclopentenone, 2-cyclohexenone and 2-cycloheptenone afforded the corresponding hydroalkoxylmethylated products (**3b–d**) in moderate to good yields (64–72%). Next, a series of α-substituted enones was examined. The deboronative radical conjugate

addition of **2a** to 2-pentylcyclopent-2-enone furnished the corresponding compound **3e** in a high yield and with moderate diastereoselectivity. The diastereofacial selectivity of the conjugate addition was investigated using D-carvone, and the corresponding product **3f** was obtained as a 6:4:3 mixture of diastereomers. Although the stereochemistry of the products has not yet been clarified, we expect a preferential attack of the radical from the *trans* side against the isopropenyl group, as previously reported by Suzuki and coworkers on the radical mediated conjugate addition of trialkylboranes to D-carvone.[88] In the literature, high levels of stereoselectivity in radical β-additions to carbonyls have been reported although diastereofacial control is commonly accessed by using either sterically hindered radical precursors[22] or chiral auxiliaries.[89,90,91] Next, the protocol was applied to an acyclic enone and delivered **3g** in moderate yield and good diastereoselectivity in favor of the *trans* product (relative stereochemistry confirmed by ^{1}H NMR coupling constants, see Experimental Part).



*Scheme 11. Hydroalkoxymethylation of enones (yield of isolated product). [a] 3:2 dr. *Major stereoisomer is shown*

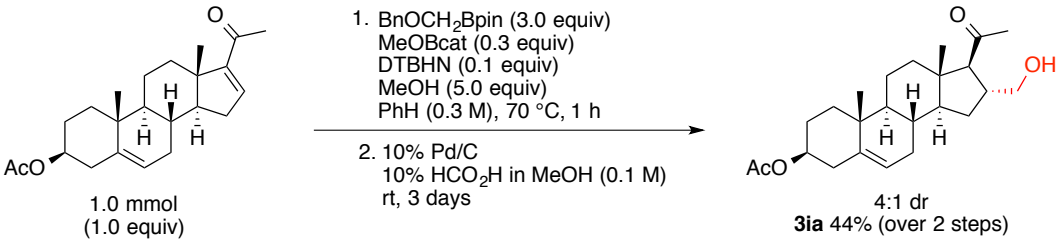
Good stereoselectivity was achieved with the steroid pregnenolone acetate **3i** which proved to be high yielding albeit three equivalents of radical precursors were required to fully consume the enone. The stereochemistry of the major isomer formed (**3i**) was determined by 2D NOESY spectroscopy, which revealed through-space correlations between H-16 and H-18, and between H-17 and H-22, confirming a *trans* relationship between the fixed stereocenter C-18 and the newly formed stereogenic center C-17, as well as between C-17 and the additional stereogenic center C-16. Ring size affected the diastereoselectivity of this process with cyclohexanone giving higher stereoselectivity compared to cyclopentenone rings. The use of electron-deficient diones was examined, and 4-cyclopentene-1,3-dione furnished the hydroalkoxymethyled compound **3h** in good yield. The regioisomer was clarified with use of single-crystal X-ray analysis (see Experimental Part).

We spent efforts to determine the limitations of the radical addition: steric hindrance near the electrophilic reaction centre completely inhibited the reaction, as expected. For example, the deboronative conjugate addition of **2a** to β-substituted enones did not deliver the corresponding products **3j–k** and the unreacted enones were almost fully recovered. The same outcome arouses when subjecting the *gem*-γ,γ-dimethylcyclohexanone (**3l**) to deboronative radical conjugate addition with **2a**. In our mechanism proposal, an enolyl radical is critical. Employing an acrylate moiety as a radical trap, as opposed to an enone moiety, should shut down the reaction. To put this mechanism test into action we attempted our radical addition to the α,β-unsaturated lactone **3m** which did indeed fail. The reaction process cannot establish a chain without the formation of the boron enolate intermediate which regenerates the 1-alkoxyalkyl radical (see Scheme 10). The physical phenomenon behind can be understood when considering spin densities. We need an oxygen-centered radical for a nucleohomolytic substitution at the boron atom in another molecule of radical precursor. For the ester, there is no localized oxygen-centered radical, being spread out over two oxygens, and consequently this radical species cannot react quickly and results in an inefficient propagation step.[92,75]

Eventually, we investigated the possibility of using the radical precursor **2a** as a limiting reagent (method **B**) to access a cost-effective approach when using more complex radical precursors. As anticipated, the use of reversed reaction conditions provided similar (sometimes even greater) yields as illustrated with the synthesis of compounds **3a**–**c** and **3g** (method **B**, 42–81%). To widen the synthetic scope of this process, the radical precursor **2b** (having a *p*-methoxybenzyl protecting group) was engaged in the deboronative radical conjugate addition using method **A** and provided the corresponding hydroalkoxylmethylated products **3ba** and **3ea**

in 81% and 77% yields, respectively. These results leave open the possibility to use different protecting group which would prove invaluable for further deprotection strategies.

As a final showcase for the synthetic utility of this method, a formal hydroxymethylation of the natural steroid precursor pregnenolone acetate was performed. On this basis, the crude residue **3i** resulting from the deboronative radical conjugate addition of **2a** to pregnenolone acetate was directly engaged in a chemoselective hydrogenation, providing the desired hydroxymethylated compound **3ia** in fairly good yield over two steps (Scheme 12). The diastereoselectivity obtained after the first step (**3i**, 4:1 dr) was not altered during the hydrogenation, providing the final hydroxymethylated compound **3ia** with a good level of stereocontrol. Interestingly, the reaction conditions proved compatible with the sensitive acetate group. Furthermore, ^{1}H and ^{13}C NMR spectroscopic analysis showed that no lactol moiety was formed after debenzylation, as confirmed by the presence of a methyl ketone (^{1}H NMR: 2.26 ppm (s, 3H, C(=O)CH_3); ^{13}C NMR (C=O): 209.9 ppm) and the absence of a lactol moiety (^{1}H NMR: ca. 1.5–1.2 ppm (s, 3H, C(=O)CH_3); ^{13}C NMR (R_2C(OH)OR): ca. 103–107 ppm), supporting the *trans* configuration of **3ai**.



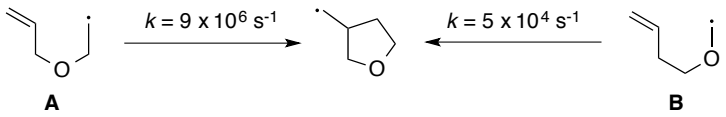
Scheme 12. Application to the hydroxymethylation of pregnenolone acetate (yield of isolated product)

5.2.2 Intramolecular radical deboronative cyclization

5.2.2.a Preliminary results

Despite being a powerful method for the preparation of tetrahydrofurans, the intramolecular cyclization of 1-(alkenyloxy)alkyl radicals remains surprisingly unexplored.[35,36,93] Therefore, in connection with our project directed toward the preparation of functionalized THF ring systems (see Chapter 4), we sought to investigate the cyclization of 1-(alkenyloxy)alkyl radicals using our previously reported radical protodeboronative conditions, i.e., with TBC and di-*tert*-butyl hyponitrite (DTBHN).

The critical part of the reaction could arise from the possible competition between intramolecular cyclization and the direct reduction of the 1-(alkenyloxy)alkyl radical by TBC. The rate constant for the reduction of secondary and primary alkyl radicals by TBC were reported (1.3×10^6 $M^{-1}s^{-1}$ at 80 °C and 6.2×10^5 $M^{-1}s^{-1}$ at 50 °C, respectively), and its use as a hydrogen donor reagent allows a sufficient time for the radical to be involved in a rearrangement before hydrogen atom transfer.[77,94] As expected, according to the high rate constant reported for the 1,5-*exo*-trig ring closure of 3-oxahex-5-enyl radicals **A** (Scheme 13),[95] Renaud and coworkers showed that these types of radicals cyclized smoothly in the presence of TBC.[94] In contrast, the rate constant for the cyclization of 2-oxa-5-hexenyl radicals **B** has been reported to be much slower (Scheme 13).[96] Beckwith and Glover reasoned that this reduced rate constant is due to the delocalization of the radical center with adjacent oxygen lone pairs, requiring an activation energy to adopt a conformational change that allows a good overlap in the chair-like transition state (TS).[97]

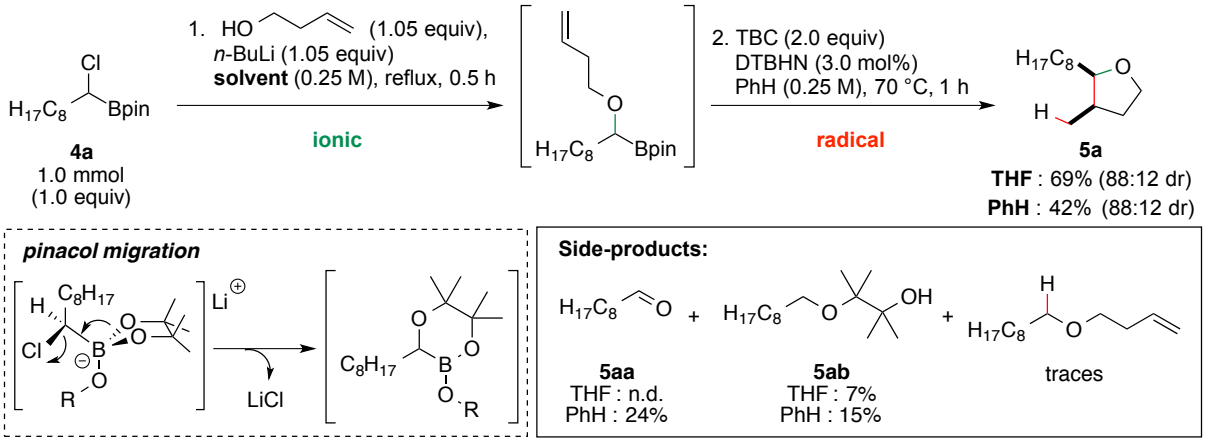


Scheme 13. Rate constants of 5-exo-trig ring closures of oxygen-containing analogues of hex-5-enyl radical at 25 °C

Keeping in mind this possible competition with the direct reduction of 1-(alkenyloxy)alkyl radicals by TBC, we started to investigate the 5-*exo*-trig ring closure of secondary radicals.

For our initial studies, the simple 1-chloroalkyl pinacol boronic ester **4a** was prepared and engaged in a 1,2-metalate shift with an *in situ* prepared lithium but-3-enolate to generate the corresponding 1-(alkenyloxy)alkyl pinacol boronic ester intermediate. Consecutively, a 5-*exo*-trig ring closure was achieved by treatment of the intermediate with TBC and DTBHN to furnish compound **5a** (Scheme 14). Aiming at performing a one-pot protocol, our initial efforts were directed towards the use of a suitable solvent for both processes. However, when using benzene, a moderate yield for **5a** was obtained over the two steps, supported by the isolation of **5aa** and **5ab**. We attributed this outcome to the formation of a 6-membered ring boronic ester, formed by *O*-migration of the pinacol over *O*-migration of the butenolate (Scheme 14, dashed frame). This assumption was supported by ^{11}B NMR analysis of the 1,2-metalate shift, in which a typical signal at 30 ppm was detected. To suppress the competitive *O*-migration of the butenolate, a systematic screening of reaction parameters was performed (see Experimental Part). Eventually, the formation of 1-(alkenyloxy)alkyl pinacol boronic ester in THF followed

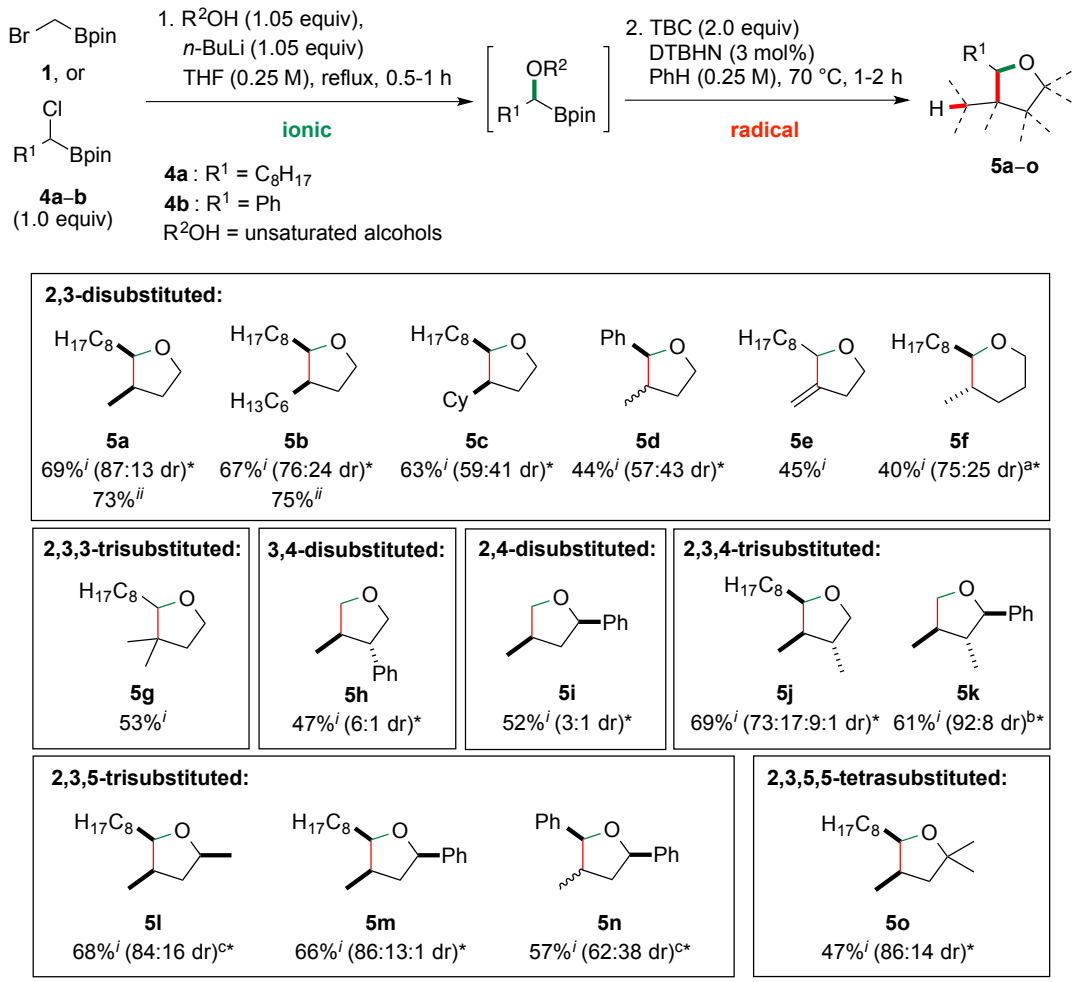
by a solvent switch to benzene to conduct the deboronative radical cyclization delivered **5a** in good yield. Recently, Aggarwal and Fasano reported a new model to explain the stereocontrol outcome and the competition between *C*- and *O*-migrations in stereospecific Matteson homologations.[98] Previously based on steric effects,[99,100] they proposed that in the presence of $ZnCl_2$, a favored *C*-migration occurs by antiperiplanar alignment of the migrating group (alkyl group) to the chloride leaving group in the TS, which benefits from attractive chelation between the latter and the metal center, and from electrostatic interaction between one of the chlorine atom of the Lewis acid and the hydrogen atom adjacent to the boron center. Such interactions could be exploited in our system to favor the *C*-migration of the boron ate-complex, and will be investigated eventually.



*Scheme 14. Synthesis of **5a** via a 1,2-metalate shift and protodeboronative radical cyclization sequence (yield of isolated product)*

5.2.2.b Scope of the reaction

Under the optimized reaction conditions, various 1-(alkenyloxy)alkyl pinacol boronic ester were generated and subjected to the deboronative intramolecular radical cyclization (Scheme 15). When the alkene was mono-, 1,2-di-, or trisubstituted, the corresponding 2,3-disubstituted THFs **5a–c** were isolated in good yields (63–69%). In all cases, the formation of the *cis*-isomers occurred preferentially, as expected from the Beckwith-Houk model.[95,101]



*Scheme 15. Scope of the radical deboronative cyclization to furnish **5a–o**. [i] Yield of isolated product (1.0 mmol scale). [ii] Yield determined by quantitative GC analysis. [a] Isolated as a mixture with 40% of the reduced 1-(alkenyloxy)alkyl radical. [b] Using a diastereoenriched R^2OH (see Experimental Part, **SI-8**). [c] Both diastereomers are with cis-configured phenyl groups. *The major diastereomer is shown and is always consistent with the Beckwith-Houk TS-model (see Scheme 16)*

The 5-*exo*-trig cyclization of the monosubstituted substrate (**5a**) gave significantly higher diastereoselectivity compared to 1,2-di- and trisubstituted homoallylic ethers derivatives, suggesting that steric repulsion generated by the two alkyl chains in pseudoequatorial positions may disfavor *cis*-isomers formation. This trend was also supported by the poor diastereoselectivity observed when using the 1-(alkenyloxy)phenyl pinacol boronic ester bearing a monosubstituted alkene (**5d**). The lower yield obtained for the formation of **5d** might be a result of the higher stability of the benzylic radical intermediate due to resonance effects. Next, the protocol was extended to the synthesis of 3-methylene-2-octyltetrahydrofuran **5e**. However, this 5-*exo*-dig ring closure gave a moderate yield. Eventually, a 6-*exo*-trig ring

closure was evaluated and provided promising results considering its lower rate constant (5.4×10^3 s^{-1} for 6-heptenyl radical) compared to 5-*exo*-trig ring closure (2.3×10^5 s^{-1} for 5-hexenyl radical),[95] and considering the absence of an accelerating Thorpe–Ingold effect (**5f**). In this example, a good conversion (80%) of the radical precursor was supported by isolation of the reduced 1-(alkenyloxy)alkyl radical. No product of 7-*endo*-trig ring closure was detected as expected from kinetically favored *exo*-trig cyclizations over *endo*-trig ring closures.[102]

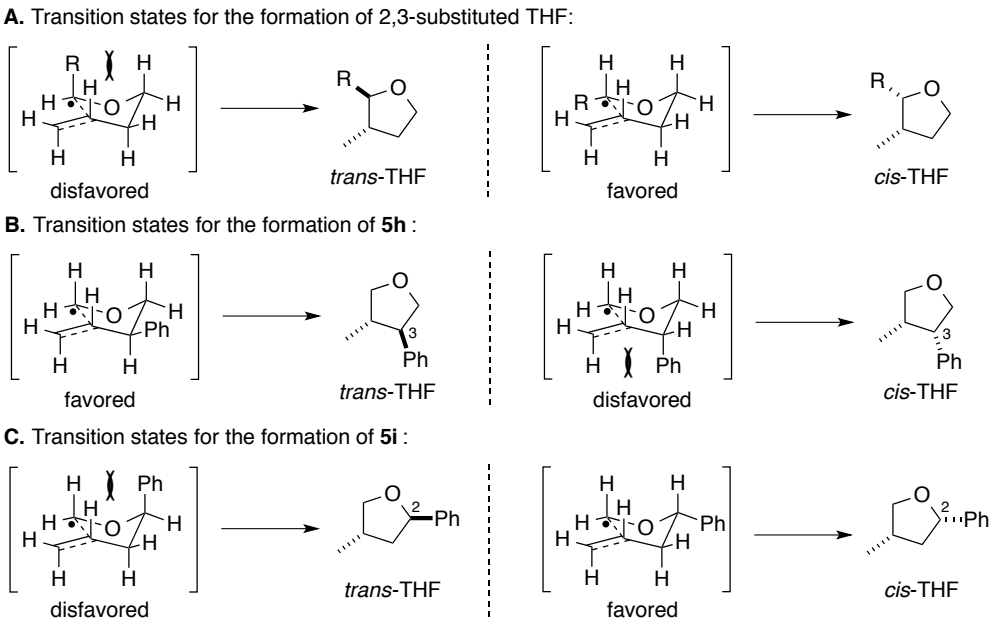
Next, the radical cyclization was examined on a highly encumbered 1,1-disubtituted alkene (**5g**). In this case, competition between 5-*exo*-trig and 6-*endo*-trig cyclization was expected as a consequence of the low rate constants for 1,5-cyclizations in the presence of an olefinic substituent,[102,103] but in contrast to the all carbon system, no *endo*-cyclized product was identified.[95] To further study the influence of substitution pattern on the diastereoselectivity of the process, we examined the cyclization of primary 1-(alkenyloxy)methylene radicals having a phenyl substituent either at the allylic or at the homoallylic position.

When substituted at the allylic position, the cyclized compound **5h** was obtained in good diastereoselectivity although in modest yield. In contrast, substitution at the homoallylic position gave the corresponding 2,4-disubstituted THF **5i** with a significantly lower diastereoselectivity control. The influence of substitution at the 3-position of the ring was further highlighted on the 5-*exo*-trig radical addition of a secondary 1-alkoxyalkyl radical to an allylic substituted alkene (**5j**). Furthermore, when we examined the cyclization of a diastereoenriched 1-(alkenyloxy)methylene pinacol boronic ester prepared from (1*R*,2*R*)-2-methyl-1-phenylbut-3-en-1-ol (98:2 dr, see **SI-8**), the formation of the 2,3,4-trisubstituted THF **5k** was observed in excellent diastereoselectivity. This example amplifies the influence of 1,3-diaxial-type interactions which result from the preferential chair-like TS having its substituents orienting in pseudoequatorial positions (Scheme 16, **A** and **B**).

The high selectivity of the cyclization process was further demonstrated on the synthesis of the all *cis* 2,3,5-trisubstituted THF ring systems **5l–m**. However, as it was observed with compound **5d**, the diastereoselectivity of **5n** was strongly affected by the presence of a phenyl ring at the 2-position (adjacent to the oxygen atom). In these cases, the TS for 5-*exo*-trig cyclizations are affected by greater steric interactions between the phenyl and the methylene groups in the pseudoequatorial positions which drives the methylene groups in the pseudoaxial positions.

Eventually, an encumbered homoallylic *gem*-dimethylated alcohol was engaged in the sequence and the corresponding 2,3,5,5-tetrasubstituted THF **5o** was delivered with good diastereocontrol.

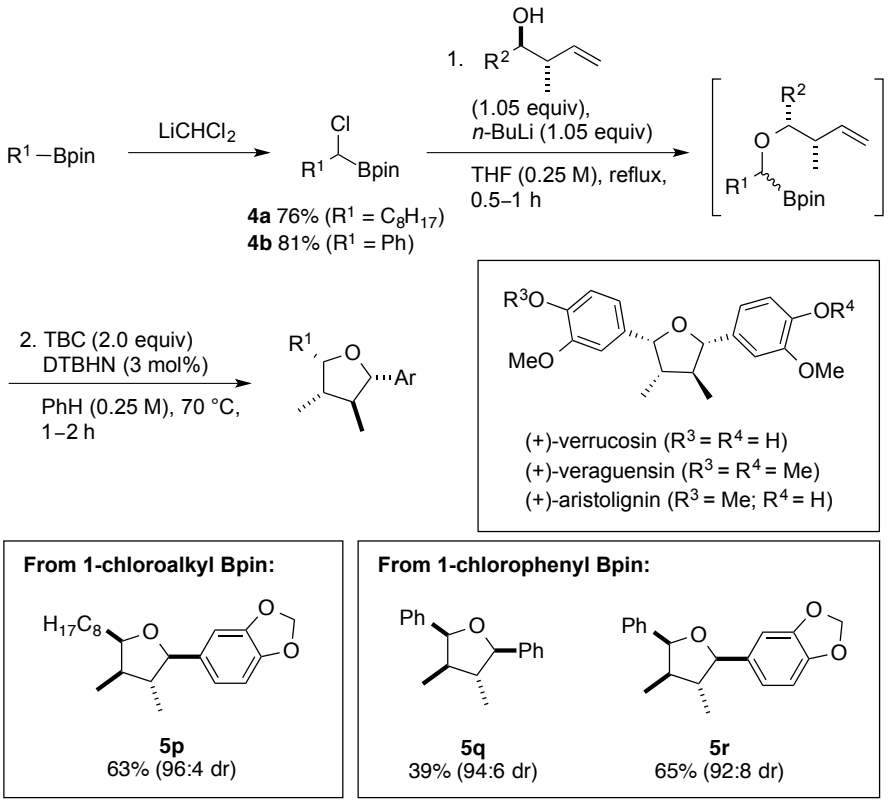
The good levels of diastereoselectivity observed for 2,3-disubstituted THF compounds can be rationalized by a chair-like TS proposed by Beckwith and Houk (Scheme 16, **A**).[95,101] According to calculations, the major product would arise from *cis*-cyclization in which the substituents occupy a pseudoequatorial position, minimizing 1,3-diaxial interactions. The shorter bond lengths in chair-like TS containing an oxygen atom would increase the strain on the forming ring, providing higher *cis*-selectivities than the all-carbon analogues.[93] 1,3-Diaxial interactions between the position C-2 and C-5 would be as well increased by the presence of an oxygen atom, inducing a preferential pseudoequatorial conformation of the substituents.



Scheme 16. Chair-like TS of oxacycle formation (boat-like TS not shown)

In contrast, when a primary radical undergoes cyclization, the shorter bond lengths of such systems are not involved in the stereocontrol of the ring closure. As expected, we noticed a better diastereoselective outcome with a substituent at the C-3 position compared to the C-2 position (Scheme 16, **B** and **C**). The substituents of the major product **5h** would adopt a *trans* conformation in which they both occupy a pseudoequatorial position, minimizing 1,3-allylic strain.

Finally, we focused our attention on the synthesis of 2,3,4,5-tetrasubstituted THF **5p–r** (Scheme 17). In each case, the homoallylic alcohol was prepared using a diastereoselective crotylation with *trans*-crotyl pinacol boronic ester. As expected, the sequence afforded the corresponding 2,3,4,5-tetrasubstituted THF **5p–r** in satisfactory yields (39–65%) and with high levels of diastereoselectivity. The relative stereochemistry of **5q** was confirmed by nOe spectroscopy (see Experimental Part). In our hands, this one-pot 1,2-metalate shift/radical deboronative intramolecular cyclization sequence demonstrated high levels of diastereoselectivity, providing a simple and practical access to complex molecules. This work may accelerate the development of densely functionalized THF-containing drug leads or natural products, as exemplified by the lignans (+)-verrucosin, (+)-veraguensin and (+)-aristolignin.



*Scheme 17. Highly diastereoselective preparation of 2,3,4,5-tetrasubstituted THF **5p–r** related to lignan natural products. Yield of isolated product (1.0 mmol scale)*

5.3 Conclusion

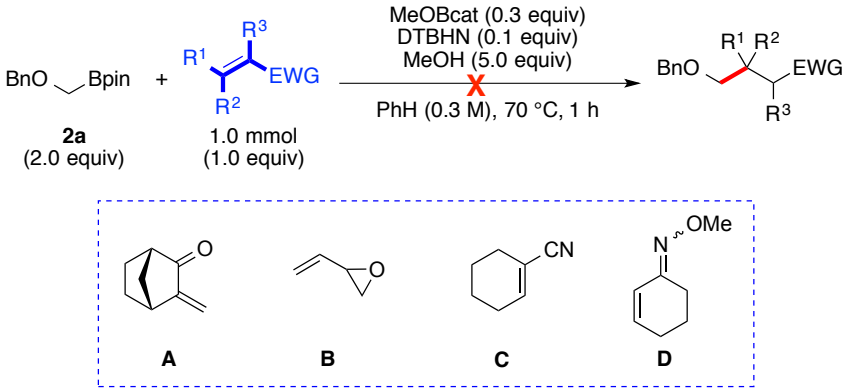
In summary, we have developed a simple and efficient protocol for the generation of 1-alkoxyalkyl radicals using readily available and stable pinacol boronic ester as precursors. Activation of the radical inactive R–Bpin via transesterification with boric ester MeO–Bcat or TBC and subsequent nucleohomolytic substitution at boron with an oxygen-centered radical afforded 1-alkoxyalkyl radicals under metal-free and non-oxidative conditions. Besides providing a practical and efficient access to alkoxymethyl radical equivalents, this method also allows the diastereoselective synthesis of 2,3,4,5-tetrasubstituted THF ring systems. Hence, the rich chemistry of boronic esters with radical reactions is likely to be of broad interest and utility for the synthesis and derivatization of ether-containing complex target molecules such as natural products and other pharmacologically relevant compounds.

5.4 Additional results

5.4.1 Hydroalkoxymethylation

5.4.1.a Scope limitations

As shown in Scheme 18, this method has currently defined limitations. Surprisingly, when 3-methylene-2-norbornanone **A** was treated under our reaction conditions, only traces of hydroalkoxymethylated product were observed although the starting enone was fully consumed. In this example, enolate formation may be less facile due to ring strain thereby resulting in polymerization of the carbon centered radical.



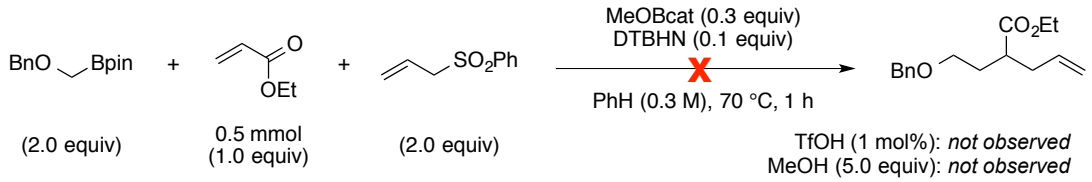
Scheme 18. Unsuccessful hydroalkoxymethylation reactions

Since trialkyboranes have proved to be versatile reagents to undergo a variety of 1,4-addition processes,[104] we wanted to extend our approach to new systems such as allylic epoxides, aldoximes and α,β-unsaturated nitriles. Surprisingly, no product of 1,4 addition was detected using 2-vinyloxirane **B** as a radical trap, and only unreacted **2a** along with benzyl methyl ether (BnOMe) were observed in the crude residue (typical chemical shifts of BnOMe identified by ^{1}H NMR: 4.47 ppm (s, 2H, PhC$\underline{H_2}$), 3.39 ppm (s, 3H, O$\underline{CH_3}$)). This outcome is presumably resulting from a polarity mismatch between the two nucleophilic species. Next, we turned our attention to the use of aldoximes and α,β-unsaturated nitriles as electrophilic radical acceptors. Since such radical traps involve the formation of a transient aminyl radical upon 1,4-addition, we thought that an amino-boron intermediate formed by nucleohomolytic substitution of the N-centered radical at boron could be involve in the radical chain process. On this basis, cyclohexene-1-carbonitrile **C** as well as a E:Z (1:0.3, ^{1}H NMR ratio) mixture of cyclohexanone-*O*-methyloxime **D** were evaluated but turned out to be unsuccessful.

5.4.2 Three-components reaction

5.4.2.a Preliminary results

Next, we investigated the feasibility of a three-components coupling reaction involving a 1,4-addition and subsequent trapping of the enolyl radical with a sulfone-based radical trap. As such, we explored the use of an acrylate as a radical acceptor for conjugate addition, in order to prevent the competitive formation of a boron-enolate prior to the trapping of the enolyl radical. We designed a one-pot protocol based on an acid catalyzed boron-transesterification to generate an *in situ* benzyloxy methylene radical (since boron-enolate hydrolysis by methanol would not be require any further) which would undergo conjugate addition to ethyl acrylate, followed by trapping of the resulting electrophilic enolyl radical with a sulfone-based radical trap and subsequent fragmentation of the resulting β-sulfonyl radical (Scheme 19). In this case, the formation of a phenyl sulfonyl radical could be exploited to sustain the radical chain process through nucleohomolytic substitution at boron and generation of a new transesterifying specie (i.e., $PhSO_2Bcat$).[78]

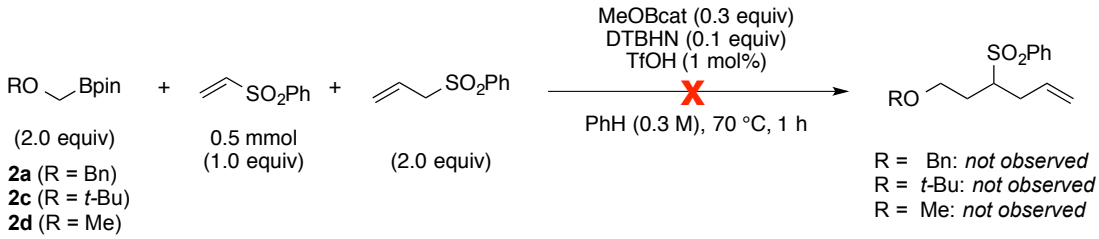


*Scheme 19. Attempted three-components reaction using **2a**, ethyl acrylate and allyl phenyl sulfone*

To our surprise, no product formation was detected and only unreacted allyl phenyl vinyl sulfone and $BnOCH_2Bpin$ along with benzyl alcohol could be identified. The same outcome arose when using the reaction conditions developed for the hydroalkoxymethylation of enones (i.e., 5.0 equivalents of MeOH, Scheme 19).

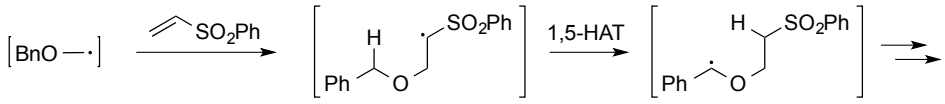
5.4.2.b Influence of the radical precursor

Therefore, we decided to explore another radical trap for conjugate addition and selected the vinyl phenyl sulfone as a more electrophilic radical trap (Scheme 20).



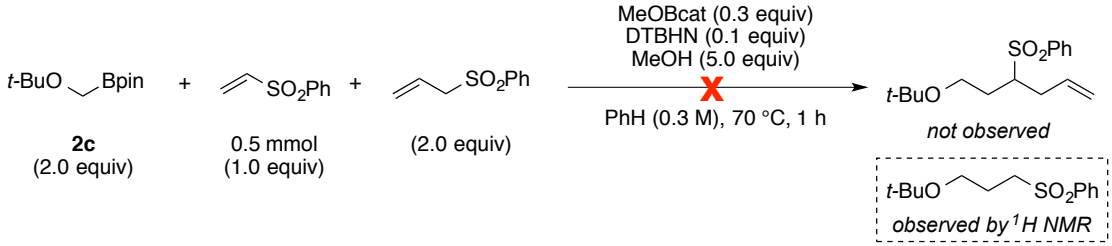
*Scheme 20. Attempted three-components reaction using **2a**, **2c–d**, vinyl phenyl sulfone and allyl phenyl sulfone*

Unfortunately, the three-components coupling product was not delivered and only unreacted starting materials were detected. During his study on free radical reactions involving α-iodoalkyl phenyl sulfones, Masnyk observed the 1,5- and 1,6-HAT from the α-sulfonyl radical center to adjacent alkyl chains.[105] Therefore, we envisioned that the transient radical formed after conjugate addition of **2a** could undergo a 1,5-HAT to generate the resonance stabilized benzylic radical, shutting down the radical chain reaction (Scheme 21).



Scheme 21. 1,5-HAT from α-sulfonyl radical center

On this basis, we prepared the *tert*-butoxy **2c** and methyloxy **2d** radical precursor analogues and evaluated the three-components reaction with vinyl phenyl sulfone and allyl phenyl sulfone as coupling partners. In practice, the radical precursors **2c** and **2d** did not provide the desired coupling product neither. Given the possible hydrolysis of the *tert*-butoxy group of **2c** under acidic catalysis, the protocol was repeated under the non-acidic reaction conditions developed for the hydroalkoxymethylation of enones (Scheme 22).

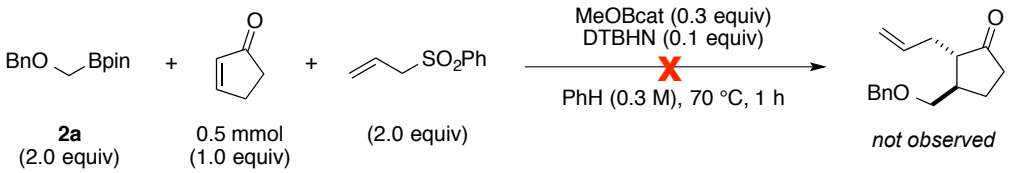


*Scheme 22. Attempted three-components reaction using **2c**, vinyl phenyl sulfone and allyl phenyl sulfone under non-acidic conditions*

In this case, we observed traces of the product of conjugate addition (yield not determined) although the desired three-component coupling compound was not detected, as supported by the recovered allyl phenyl sulfone.

5.4.2.c Via conjugate addition to enone

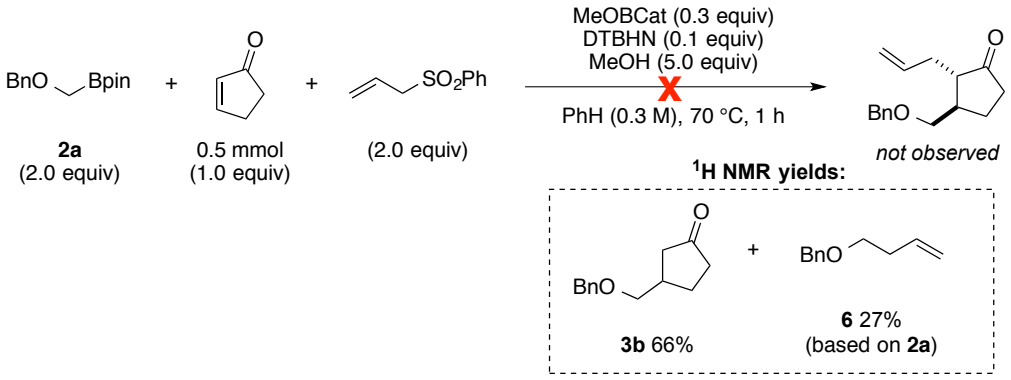
Eventually, we tested the protocol with an enone although we anticipated that fast boron-enolate formation would not allow trapping of the transient enolyl radical (Scheme 23). The three-components coupling product was not detected under these reaction conditions and only traces of hydroalkoxymethylated cyclopentenone along with unreacted allyl phenyl sulfone and **2a** were observed.



*Scheme 23. Attempted three-components reaction using **2a**, 2-cyclopentenone and allyl phenyl sulfone*

Next, the reaction was repeated with methanol and furnished exclusively the product of conjugate addition **3b** (that was not detected without MeOH, see Scheme 23) along with 27% of direct addition of the benzyloxy methylene radical onto allyl phenyl sulfone (**6**) (Scheme

24). As expected, the boron-enolate formation is faster than the trapping of the enolyl radical. In retrospect, the use of a more nucleophilic sulfonyl radical trap may have been preferred over the allyl phenyl sulfone due to the competing formation of **6**.

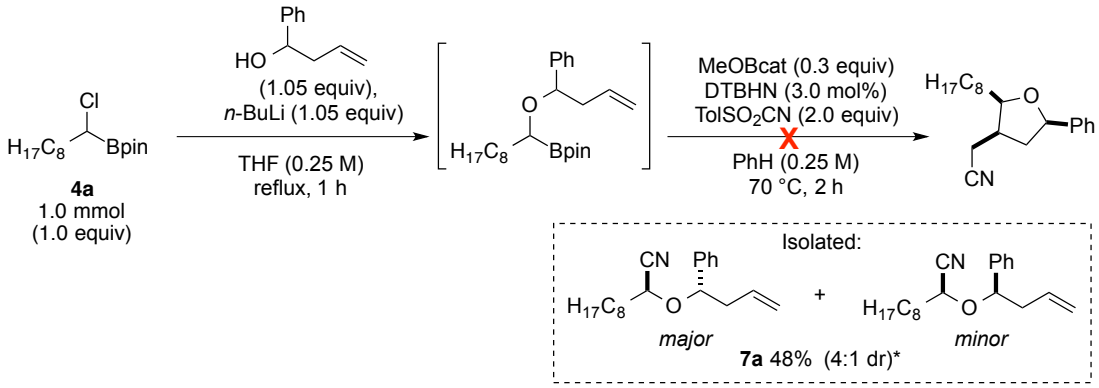


*Scheme 24. Attempted three-components reaction using **2a**, 2-cyclopentenone and allyl phenyl sulfone (^{1}H NMR yields)*

5.4.3 Diastereoselective functionalization: towards chiral auxiliary control

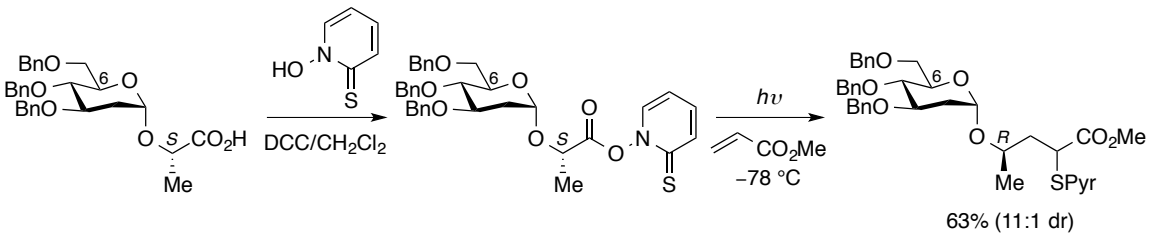
5.4.3.a Preliminary results

We next examined a sequence involving an intramolecular 5-*exo*-trig ring closure of a 1-(alkenyloxy)alkyl radical followed by trapping of the resulting primary radical with an electrophilic trap. In this context, the 1-alkoxyalkyl boronic ester prepared by a 1,2-metalate shift between **4a** and 4-phenyl-1-buten-4-ol was treated under non-reductive radical deboronative conditions, using *p*-toluenesulfonyl cyanide as a radical trap (Scheme 25). Unfortunately, no THF core was detected and the product of direct cyanation **7a** was almost exclusively obtained, albeit in moderate yields. Surprisingly, a good degree of diastereocontrol was observed for such a system.



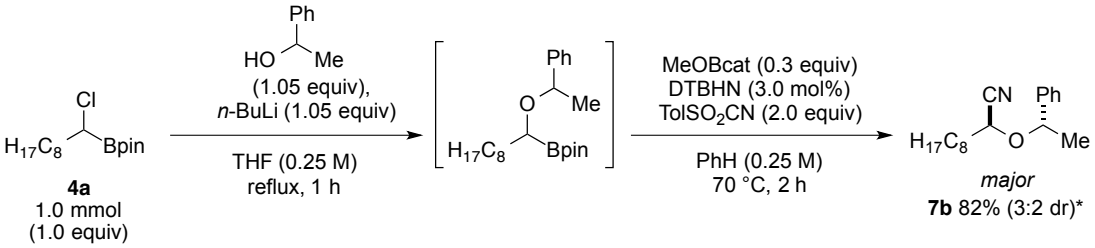
*Scheme 25. One-pot radical deboronative cyclization/cyanation sequence (yield of isolated product). *Determined by GC analysis of the crude residue*

Whereas the control of acyclic stereochemistry during radical reactions still remains a difficult task, some levels of diastereocontrols may result either from preferential conformation of the alkyl radical (e.g. through stabilizing interactions) and/or from predominant facial attack (e.g. influenced by steric effects).[106] Toward this end, both substrate- and auxiliary-derived chirality have been developed to control the stereochemical course of radical reactions.[107] Early work on the development of chiral hydroxyalkyl radical equivalents were reported from the laboratories of Garner and Greene.[107,108,109,110,111,112] For instance, high acyclic ρ-selectivities in radical addition reactions were achieved using pyranosidic chiral auxiliaries, as a consequence of substitution at C-6 (Scheme 26). Hence, the introduction of bulky substituents or chiral auxiliaries are usually required for stereoselective formations of new C—C bonds in acyclic systems.[113]



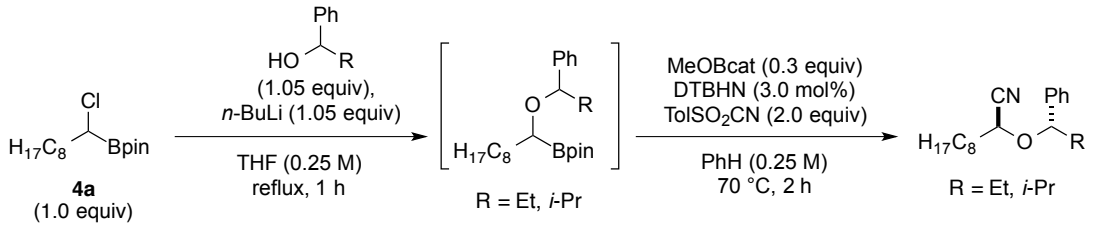
Scheme 26. Diastereoselective radical Michael reaction using Garner's chiral auxiliary

In order to see whether the promising acyclic stereocontrol observed in Scheme 25 could be enhanced by the incorporation of bulky substituents, we sought to investigate the effect of steric crowding around the benzylic carbon. Introduction of a methyl substituent has yet shown poor diastereoselectivity control in the radical reaction (Scheme 27) although **7b** was accessed in good yield.



*Scheme 27. Radical deboronative cyanation to furnish **7b** (yield of isolated product). *Determined by ^{1}H NMR analysis of the crude residue*

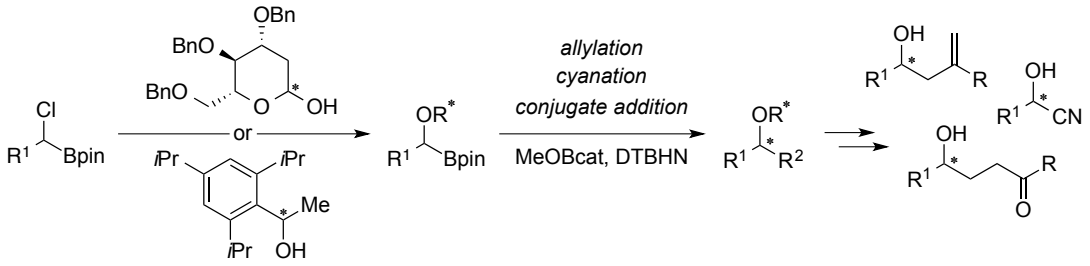
To test further this idea, various benzylic alcohols (i.e., bearing an ethyl or an isopropyl group) will be engaged in the 1,2-metalate shift/radical deboronative cyanation sequence (Scheme 28).



Scheme 28. Envisaged benzylic substituents to test the radical deboronative cyanation

5.4.3.b Outlook

There are many avenues of investigation left to explore. As aforementioned, substitution around the benzylic carbon will be given more consideration. The use of 2-deoxyglucose based auxiliary and Greene's auxiliary will be also considered to control the stereochemical course of the deboronative radical chain reaction (Scheme 29). This strategy will allow the stereoselective preparation of secondary alcohol starting from achiral α-chloroalkyl boronic esters. The ρ-selectivities of these radical reactions will also be explored using different radical traps, that are, sulfonyl radical traps (i.e., for allylation reactions) and Michael acceptors. If successful, these sequences will be of great interest for the synthesis of α-functionalized alcohol derivatives with high degrees of diastereo- and enantio- selectivities. *These investigations are now undertaken by Agathe Chambe and will therefore not be discussed further.*



Scheme 29. Envisioned stereoselective synthesis of α-functionalized alcohol derivatives

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Experimental Part

Contents

1. General and instrumentation

Glassware and reaction techniques: Unless otherwise stated, all glassware was flame-dried, cooled under vacuum, and back-filled with nitrogen (N_2) or argon (Ar); then the reactions were run under that inert atmosphere (atm) and additions of solids were performed under a positive pressure of that inert atm. Unless otherwise stated, all yields are isolated yields. Room temperatures (rt) were generally in the range 21–25 °C.

Solvents: Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (MeCN), n-hexane and benzene (PhH) for reactions were filtered through a column of dried alumina under a positive pressure of argon. *N,N*-Dimethylformamide (DMF) was purchased from Aldrich (anhydrous, 99.8% [CAS = 68-12-2]) and used as such. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. All water used for solutions, quenches, and aqueous extractions was deionized water.

Reagents and chemicals: All reagents and chemicals used were commercial and used without further purification unless specified below.

Column chromatography: All chromatographic purifications were flash (ca. 2–3 atm of pressurized air) column chromatography (FCC) on silica gel (Macherey-Nagel Silica 60, 0.04 – 0.063 mm) and/or neutral aluminium oxide (CAMAG 507 – C – I neutral).

Thin layer chromatography (TLC): Silicycle glass backed TLC extra hard layer, 259 µm, 60 Å, F-254 Silica gel 60 Å (F-254) and *Macherey-Nagel* SIL G/UV254, 0.25 mm analytical plates were used for TLC. Revelation was done firstly by non-destructive visualization under a UV lamp (254 nm); destructive revelation was performed with staining solutions of either potassium permanganate ($KMnO_4$), cerium molybdate (CAM), or cerium sulfate ($Ce(SO_4)_2$), followed by heating.

NMR: The NMR experiments were performed on a Bruker Avance-300 spectrometer operating at a resonance frequency of 300.18 MHz for ^{1}H nuclei, 75.48 MHz for ^{13}C and 96 MHz for ^{11}B nuclei. ^{11}B NMR spectra were calibrated using $Et_2O.BF_3$ (0.0 ppm) as an external reference. Chemical shifts are reported in units of δ (ppm) using the internal standard residual $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR spectra and δ = 77.16 ppm for ^{13}C NMR spectra), or DMSO-d6 (δ = 2.50 ppm for ^{1}H NMR spectra and δ = 39.52 ppm for ^{13}C NMR spectra), or TMS (δ = 0.00 ppm for ^{1}H NMR spectra and δ = 0.00 ppm for ^{13}C NMR spectra). Due to coupling to the quadrupolar ^{11}B and ^{10}B nuclei, the carbons linked to boron atoms generally give a broad signal in ^{13}C NMR and are usually not detectable. The following abbreviations were used to explain the

multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sep = septet, m = multiplet, app = apparent. Referencing and common impurities were assigned by common standards.[1,2]

Procedure for the determination of yields by ^1H NMR: NMR yields were determined using 1,4-dimethoxybenzene (s, 6.74 ppm, 4H; s, 3.67 ppm, 6H) as an internal standard. The standard was added to the crude residue after work-up, dissolved in $CDCl_3$ by swirling and sonication for 5 minutes in order to have a homogenous mixture, and an aliquot was taken to be analyzed by ^1H NMR.

GC: GC analyses were carried out on a Thermo Electron Trace GC ULTRA instrument fitted with a Macherey-Nagel Optima delta-3-0.25 µm capillary column (20 m, 0.25 mm). Gas carrier: He 1.4 mL/min; injector: 220 °C split mode; detector: FID 280 °C, H2 35 mL/min, air 350 mL/min. Infrared spectra were recorded on a Jasco FT/IR-4700 Spectrometer and are reported in wave numbers (cm^{-1}).

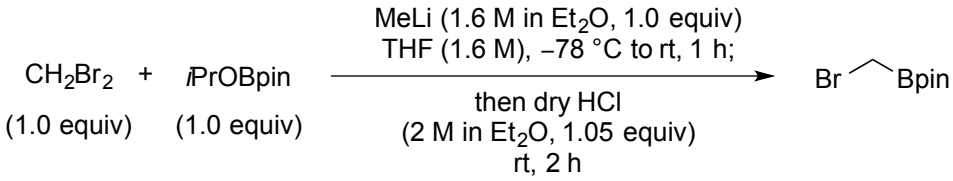
GC yields were determined using *n*-pentadecane [CAS = 629-62-9] as an internal standard. A sample was taken from the reaction mixture, worked-up, filtered through neutral aluminium oxide and diluted with ethyl acetate (EtOAc) before being injected on the GC instrument. The percent yield was calculated by experimental determination of relative response factors (RRFs).

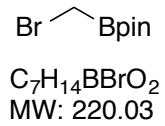
MS: HRMS analyses and elemental composition determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using Electron Spray Ionization (ESI) and Nanospray Ionization (NSI) mode at the University of Bern. When ESI and NSI was not sufficient to ionize the molecule, HRMS was performed at the University of Zürich with a Bruker maXis QTof high resolution mass spectrometer (APCI mode) and Thermo DFS (ThermoFisher Scientific) double-focusing magnetic sector mass spectrometer (EI and CI modes).

IR: Infrared spectra were recorded neat equipped with a diamond ATR System and are reported in wave numbers (cm^{-1}).

2. Experimental Procedures and Characterizations for the Synthesis of Reagents and Substrates

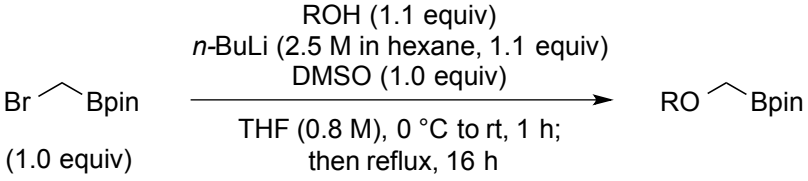
2.1 Synthesis of 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1)





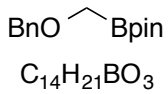
$BrCH_2Bpin$ was prepared according to a slightly altered literature procedure.[3,4] To a three-necks, 250 mL round-bottom flask equipped with a 100 mL dropping funnel and a low-temperature thermometer was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.5 mL, 50.0 mmol, 1.0 equiv), dibromomethane (3.48 mL, 50.0 mmol, 1.0 equiv) and THF (30 mL, 1.6 M) with vigorous stirring. The reaction mixture was cooled to –78 °C and the methyllithium solution[5] (31.3 mL, 50.0 mmol, 1.6 M solution in Et_2O, 1.0 equiv) was loaded into the dropping funnel and added dropwise over 30 minutes, maintaining the temperature below –65 ºC. The reaction mixture was then stirred at this temperature for another hour and the cooling bath removed. After 1 h at rt, dry HCl (26.0 mL, 2.0 M in Et_2O, 1.05 equiv) was added at once and the reaction mixture was stirred for 2 h. The volatiles were removed *in vacuo* (attention: MeI – perform in a well-ventilated fume-hood). The residue was diluted in *n*-pentane (100 mL) and washed with water (100 mL), sat. aq. $NaHCO_3$ (100 mL), sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was vacuum distilled (82–85 °C head, 6.7×10^{-2} mbar) to afford **1** as a colorless oil (3.05 g, 14.0 mmol, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 2H), 1.27 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.6, 24.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) calcd. for $C_7H_{14}O_2BBr$ $[M]^+$: 220.0264; found: 220.0265.

2.2 General Procedure 1 (GP1): Synthesis of 1-alkoxymethyl pinacol boronic esters 2a–d



To a two-necks, 250 mL round-bottom flask equipped with a condenser was added the resulting alcohol (1.1 equiv) and THF (0.8 M). The solution was cooled to 0 °C before dropwise addition of *n*-butyllithium (2.5 M in hexane, 1.1 equiv). After 5 minutes of stirring, 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv) and DMSO (1.0 equiv) were added in sequence and the resulting mixture was stirred at rt for another hour and then heated under reflux for 16 h. The contents were partitioned between TBME (100 mL) and water (100 mL). The two phases were separated and the aqueous phase was back-extracted with TBME (2×100 mL). The combined ethereal phase was washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

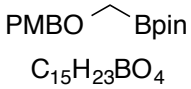
2-((Benzyloxy)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2a)



$C_{14}H_{21}BO_3$
MW: 248.16

From **1** (10.0 g, 40.5 mmol) and benzyl alcohol (4.7 mL, 44.6 mmol) following **GP1**. The crude residue was purified by FCC on silica gel (*n*-pentane/TBME 8:2) to afford **2a** as a colorless oil (7.13 g, 28.8 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 4.52 (s, 2H), 3.28 (s, 2H), 1.28 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.7, 84.0, 75.9, 24.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.5. IR (neat): 2977, 2849, 1371, 1337, 1239, 1091 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{22}O_3B$ $[M+H]^+$: 249.1657; found: 249.1653.

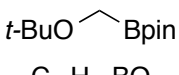
2-(((4-Methoxybenzyl)oxy)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2b)



$C_{15}H_{23}BO_4$
MW: 278.17

From **1** (2.2 g, 10.0 mmol) and *p*-methoxy benzyl alcohol (1.4 mL, 11.0 mmol) following **GP1**. The crude residue was purified by vacuum distillation (58 – 61 °C head, 2 mbar) to afford **2b** as a colorless oil (2.0 g, 7.2 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 6.88 – 6.85 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.24 (s, 2H), 1.27 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 130.4, 130.0, 113.8, 84.0, 75.5, 55.4, 24.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.5. IR (neat): 2977, 2836, 1612, 1511, 1371, 1337, 1241, 1170, 1142, 1083, 1033 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{22}O_4B$ $[M-H]^+$: 277.1606; found: 277.1613.

2-(*tert*-Butoxymethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)

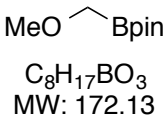


$C_{11}H_{23}BO_3$
MW: 214.17

From **1** (5.0 g, 22.7 mmol) and *tert*-butyl alcohol (2.4 mL, 25.0 mmol, distilled over CaH_2 prior to use) following **GP1**. The crude residue was purified by FCC on silica gel (*n*-pentane/TBME 8:2) to afford **2c** as a colorless oil (2.72 g, 12.7 mmol, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (s, 2H), 1.27 (s,

12H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.8, 73.4, 27.1, 24.9. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.7. IR (neat): 2975, 1362, 1337, 1194, 1144, 1078, 968, 847 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{24}O_3B$ $[M+H]^+$: 215.1813; found: 215.1809.

2-(Methoxymethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2d)



$C_8H_{17}BO_3$
MW: 172.13

From **1** (5.0 g, 22.7 mmol) and methanol (1.0 mL, 25.0 mmol, dried over molecular sieves 4Å prior to use) following **GP1**. The crude residue was purified by vacuum distillation (62 – 65 °C head, 4 mbar) to afford **2d** as a colorless oil (1.06 g, 7.0 mmol, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3H), 1.28 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.0, 62.2, 24.8. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.3. IR (neat): 2979, 1372, 1337, 1253, 1144, 1110, 846, 674 cm^{-1}. HRMS (ESI) calcd. for $C_8H_{18}O_3B$ $[M+H]^+$: 173.1344; found: 173,1346.

2.3 Synthesis of DTBHN and MeOBcat

Di-*tert*-butyl hyponitrite (DTBHN)

t-BuON=NO*t*-Bu

$C_8H_{18}N_2O_2$
MW: 174.24

DTBHN was prepared according to a slightly altered literature procedure.[6] A three-neck, 250 mL round-bottom flask equipped with a stirring bar was loaded sodium *trans*-hyponitrite hydrate (8.15 g) which was then dried to constant weight (5.58 g). In another flask, $ZnCl_2$ hydrate (14 g) was melted under stirring *in vacuo* (thrice) in order to dry it. From the resulting block of grey solid, pieces with a total weight of 8.6 g (63.1 mmol, 1.2 equiv) were (quickly) transferred into a two-neck flask, dried another 10 minutes under vacuum, and then suspended in Et_2O (35 mL) first with stirring for 2 h then with sonication for another 20 minutes until no more pieces of $ZnCl_2$ were visible. To the dry hyponitrite was added Et_2O (30 mL) and *tert*-butylbromide (47 mL, 418 mmol, 8.0 equiv) and the resulting milky white mixture was cooled to –10 °C (internal temperature) using an ice/NaCl/water bath. Then, the $ZnCl_2$ suspension was transferred into the reaction vessel with the hyponitrite using a cannula (Ø = 1 mm) at a rate that the internal temperature did not exceed –5 °C. After complete addition, the mixture was allowed to reach rt and stirred for another 1.5 h at this temperature. The reaction mixture was filtered and the remaining solid was washed with Et_2O (3×10 mL). The resulting yellow solution was transferred into a separatory funnel and water was added. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4 and the volatiles

were removed under reduced pressure (bath temperature 20 °C, 400 mbar, end to 50 mbar for a short time). The obtained solid was crystallized from *n*-pentane to furnish almost colorless crystals in three crops (all crops were washed with cold *n*-pentane). Recrystallization from *n*-pentane of the combined crops furnished the product as colorless, transparent crystals (3.43 g, 37%). DTBHN was stored for months at 4 °C. Spectral and physical data were in accordance with the literature.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.2, 27.8.

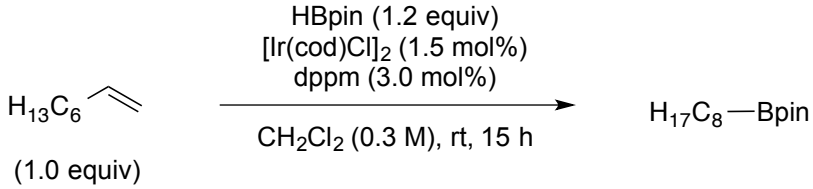
2-Methoxybenzo[*d*][1,3,2]dioxaborole (MeOBcat)

MeOBcat
$C_7H_7BO_3$
MW: 150.05

A one-neck, 100 mL round-bottom flask was charged with catecholborane (4.0 mL, 37.5 mmol, 1.0 equiv) and benzene (25 mL, 1.5 M). MeOH (1.52 mL, 37.5 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred at rt until no more H_2 evolution was visible (ca. 1 h). The solvent was removed under reduced pressure and the residue was distilled under vacuum (42 – 45 °C head, 4×10^{-2} mbar) to afford MeOBcat as a colorless oil (3.2 g, 21.1 mmol, 57%). Spectral and physical data were in accordance with the literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.59 (m, 2H), 6.48 – 6.42 (m, 2H), 3.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 121.1, 110.8, 51.7. ^{11}B NMR (96 MHz, $CDCl_3$) δ 23.4.

2.4 Iridium catalyzed hydroboration of 1-octene to furnish SI-1

4,4,5,5-Tetramethyl-2-octyl-1,3,2-dioxaborolane (SI-1)

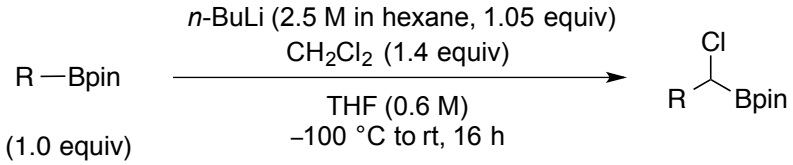


$H_{17}C_8$–BPin
$C_{14}H_{29}BO_2$
MW: 240.23

A one-neck, 250 mL round-bottom flask was charged with $[Ir(cod)Cl]_2$ (403 mg, 0.6 mmol, 1.5 mol%) and methylenebis(diphenylphosphine), dppm (461 mg, 1.2 mmol, 3.0 mol%) in a glove-box. CH_2Cl_2 (130 mL, 0.3 M), pinacolborane (7.0 mL, 48.0 mmol, 1.2 equiv), and 1-octene (6.3 mL, 40.0 mmol, 1.0 equiv) were added in sequence at 0 °C and the contents were stirred at rt for 15 h. The reaction mixture was quenched with MeOH (1 mL/mmol) and water (3 mL/mmol) and then diluted with Et_2O (4 mL/mmol). The two phases were separated and the aqueous phase

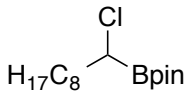
was back-extracted with Et_2O (2×50 mL). The collected ethereal phases were washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (CH_2Cl_2 100%) to afford **SI-1** as a colorless oil (8.94 g, 37.2 mmol, 93%). Spectral and physical data were in accordance with the literature.[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 – 1.35 (m, 2H), 1.30 – 1.24 (m, 22H), 0.89 – 0.85 (m, 3H), 0.77 (app t, *J* = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.8, 32.5, 31.9, 29.4, 29.3, 24.8, 24.0, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.1.

2.5 General Procedure 2 (GP2): Synthesis of 1-chloroalkyl pinacol boronic esters 4a and 4b[10]



A one-neck, 250 mL round-bottom flask was charged with CH_2Cl_2 (1.4 equiv) and THF (0.6 M) and the contents were cooled to –100 °C using a 95% ethanol/liquid N_2 slush bath. *n*-Butyllithium (2.5 M in hexane, 1.05 equiv) was added dropwise by bringing the tip of the syringe needle to within about 5 mm of the surface of the cold solution. After 30 minutes, a solution of alkyl pinacol boronic ester (1.0 equiv) in Et_2O (2 mL) was added in one portion and the contents were allowed to warm to rt and stir for 16 h. CH_2Cl_2 was added to precipitate the lithium chloride. The solution was filtered over cotton, and the volatiles were removed *in vacuo*.

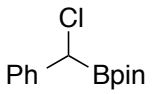
2-(1-Chlorononyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4a)



$C_{15}H_{30}BClO_2$
MW: 288.20

From **SI-1** (5.76 g, 24.0 mmol) following **GP2**. The crude residue was purified by vacuum distillation (83 – 86 °C head, 1×10^{-2} mbar) to afford **4a** as a colorless oil (5.24 g, 18.2 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (dd, *J* = 7.9, 6.9 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.50 – 1.24 (m, 24H), 0.88 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.3, 34.1, 31.9, 29.4, 29.2, 29.1, 27.3, 24.61, 24.58, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.4. IR (neat): 2978, 2924, 2854, 1380, 1372, 1340, 1140, 967, 847, 673 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{30}O_2BClNa$ $[M+Na]^+$: 311.1919; found: 311.1920.

2-[Chloro(phenyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4b)

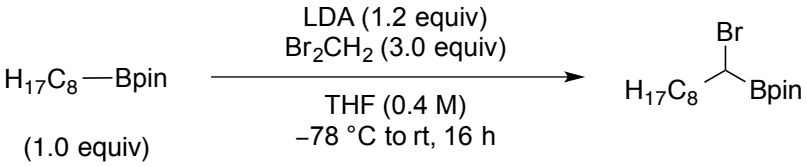


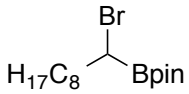
$C_{13}H_{18}BClO_2$
MW: 252.11

From 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (2.35 g, 11.5 mmol) following **GP2**. The crude residue was purified by vacuum distillation (118 – 121 °C head, 2 mbar) to afford **4b** as a colorless oil (2.35 g, 9.3 mmol, 81%). Spectral and physical data were in accordance with the literature.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.38 – 7.24 (m, 3H), 4.48 (s, 1H), 1.28 (s, 6H), 1.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.7, 128.5, 127.8, 84.8, 24.53, 24.52. ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.9.

2.6 Synthesis of 2-(1-bromononyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane SI-2[12]

2-(1-Bromononyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-2)



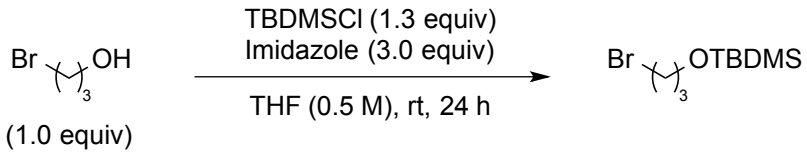


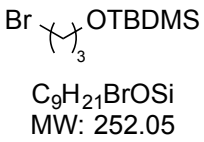
$C_{15}H_{30}BBrO_2$
MW: 332.15

In a one-neck, 100 mL round-bottom flask was prepared a solution of lithium diisopropylamide (LDA) by addition of *n*-butyllithium (5.10 mL, 12.0 mmol, 2.35 M in hexane, 1.2 equiv) to a solution of diisopropylamine (1.84 mL, 13.0 mmol, 1.1 equiv) in THF (16 mL, 0.8 M) at –78 °C. The resulting mixture was warmed to 0 °C. To another one-neck, 250 mL round-bottom flask was added **SI-1** (2.4 g, 10.0 mmol, 1.0 equiv), dibromomethane (2.01 mL, 30.0 mmol, 3.0 equiv) and THF (10 mL, 1.0 M) and the contents were cooled to –78 °C. The LDA solution was then added dropwise at –78 °C. The reaction mixture was kept at –78 °C for 10 minutes and then stirred at rt for 16 h. The contents were diluted with Et_2O (50 mL) and quenched with sat. aq. NH_4Cl (100 mL). The aqueous phase was back-extracted with Et_2O (3×30 mL) and the collected ethereal phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by vacuum distillation (134–137 °C head, 1×10^{-2} mbar) to afford **SI-2** as a colorless oil (1.83 g, 5.5 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (t, J = 7.9 Hz, 1H), 1.92 – 1.85 (m, 2H), 1.49 – 1.24 (m, 24H), 0.88 (app t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.1, 34.1, 31.9, 29.4, 29.2, 29.0, 28.8, 24.5, 24.4, 22.7, 14.1. ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.0. IR (neat): 2977, 2924, 2854, 1381, 1338, 1143, 966, 847, 672, 620 cm^{-1}. HRMS calcd. for $C_{15}H_{30}O_2BBrNa$ $[M+Na]^+$: 355.1406; found: 355.1414.

2.7 Synthesis of 3-Cyclohexylidenepropan-1-ol SI-6

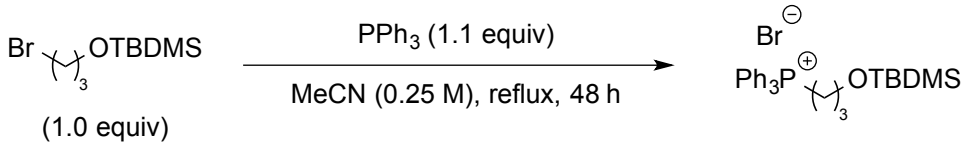
(3-Bromo-propyloxi)-*tert*-butyl-dimethylsilane (SI-3)

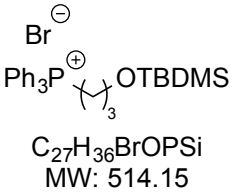




To a one-neck, 250 mL round-bottom flask containing a solution of 3-bromo-propanol (2.62 mL, 30.0 mmol, 1.0 equiv) in THF (60 mL, 0.5 M) was added imidazole (6.13 g, 90.0 mmol, 3.0 equiv) and *tert*-butyldimethylsilyl chloride (5.88 g, 39.0 mmol, 3.0 equiv) under a positive pressure of N_2 atm and the contents were stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo* and the crude residue was partitioned between EtOAc (50 mL) and water (50 mL). The two phases were separated and the aqueous phase was back-extracted with EtOAc (3×20 mL). The collected organic phase was collected and washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **SI-3** as a pale-yellow oil (7.6 g, 30.0 mmol, >99%). Spectral and physical data were in accordance with the literature.[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (t, *J* = 5.7 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.03 (p, *J* = 6.1 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.4, 35.6, 30.7, 25.9, 18.3, -5.4.

(3-((*tert*-Butyldimethylsilyl)oxy)propyl)triphenylphosphonium bromide (SI-4)

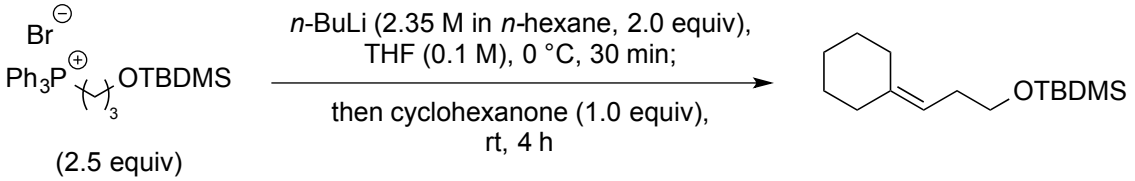


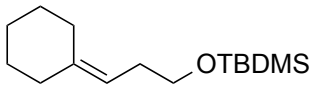


To a one-neck, 250 mL round-bottom flask containing a solution of **SI-3** (3.8 g, 15.0 mmol, 1.0 equiv) in MeCN (60 mL, 0.25 M) was added triphenylphosphine (4.3 g 16.5 mmol, 1.1 equiv) and the resulting mixture was heated under reflux for 48 h. The volatiles were removed *in vacuo* and the crude residue was triturated in Et_2O and filtered to afford **SI-4** as a white powder (7.2 g, 14.0 mmol, 93%). Spectral and physical data were in accordance with the literature.[14] ^{1}H NMR (300 MHz, DMSO-d6) δ 7.93 – 7.74 (m, 15H), 3.69 (t, *J* = 6.0 Hz, 2H), 3.59 – 3.49 (m, 2H), 1.77 – 1.69 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C

NMR (75 MHz, DMSO-d6) δ 134.9, 133.6, 133.5, 130.3, 130.1, 119.0, 117.9, 62.0, 61.8, 25.8, 25.3, 17.9, 17.6, 16.9, -5.4.

tert-Butyl(3-cyclohexylidenepropoxy)dimethylsilane (SI-5)

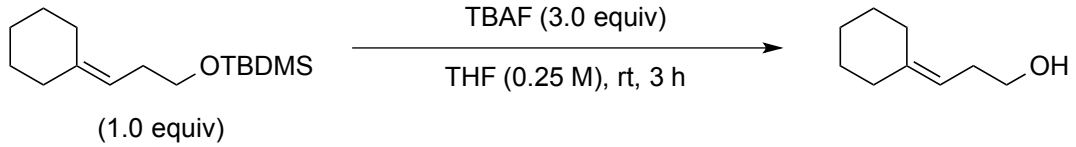


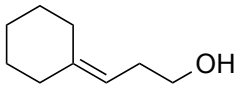


$C_{15}H_{30}OSi$
MW: 254.21

To a one-neck, 100 mL round-bottom flask containing a solution of **SI-4** (2.58 g, 5.0 mmol, 2.5 equiv) in THF (20 mL, 0.1 M) was treated with *n*-butyllithium (2.35 M in *n*-hexane, 1.70 mL, 4.0 mmol, 2.0 equiv) at 0 °C and the contents were stirred for 30 minutes at this temperature. A solution of cyclohexanone (207 µL, 2.0 mmol, 1.0 equiv) in THF (2 mL) was added and the contents were stirred at rt for 4 h. The reaction mixture was quenched carefully by addition of sat. aq. NH_4Cl (15 mL). The two phases were separated and the aqueous phase was back-extracted with EtOAc (3×5 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (*n*-pentane 100%) to afford **SI-5** as a colorless oil (509 mg, 2.0 mmol, >99%).[§] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (t, *J* = 7.3 Hz, 1H), 3.56 (t, *J* = 7.2 Hz, 2H), 2.22 (q, *J* = 7.3 Hz, 2H), 2.10 (dt, *J* = 18.0, 5.1 Hz, 4H), 1.55 – 1.49 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 117.0, 63.5, 37.2, 31.1, 28.8, 28.6, 27.9, 26.9, 26.0, 18.4, -5.2. IR (neat): 2954, 2922, 2856, 1472, 1251, 1088, 831, 773 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{28}OSi$ $[M-2H]^+$: 252.1908; found: 252.1904. [§]Contaminated with triphenylphosphine oxide.

3-Cyclohexylidenepropan-1-ol (SI-6)



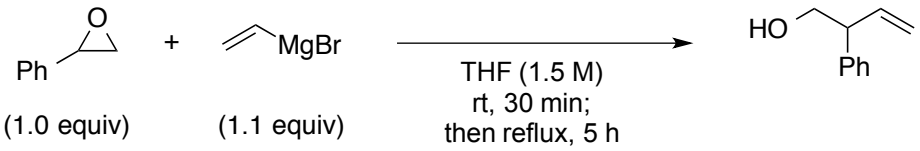


$C_9H_{16}O$
MW: 140.12

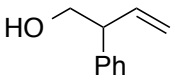
To a one-neck, 50 mL round-bottom flask containing a solution of **SI-5** (382 mg, 1.5 mmol, 1.0 equiv) in THF (6.0 mL, 0.25 M) was added TBAF (4.5 mL, 4.5 mmol, 3.0 equiv) dropwise and the contents were stirred at rt for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (5 mL). The two phases were separated and the aqueous phase was back-extracted with EtOAc (3×5 mL). The combined extracts were washed with sat. aq. NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 1:1) to afford **SI-6** as a colorless oil (188 mg, 1.3 mmol, 89%).[§] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (t, *J* = 7.4 Hz, 1H), 3.60 (q, *J* = 6.1 Hz, 2H), 2.28 (q, *J* = 6.7 Hz, 2H), 2.13 (dt, *J* = 16.3, 5.2 Hz, 4H), 1.61 – 1.47 (m, 6H), 1.41 – 1.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 116.5, 62.6, 37.3, 30.7, 28.9, 28.7, 28.0, 26.9. IR (neat): 3333, 2956, 2834, 1139, 1037, 1015, 833, 771, 732 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{16}O$ $[M]^+$: 140.1193; found: 140.1196.

[§]Contaminated with *tert*-butyldimethylsilanol.

2.8 Synthesis of 2-Phenylbut-3-en-1-ol (SI-7)[15]



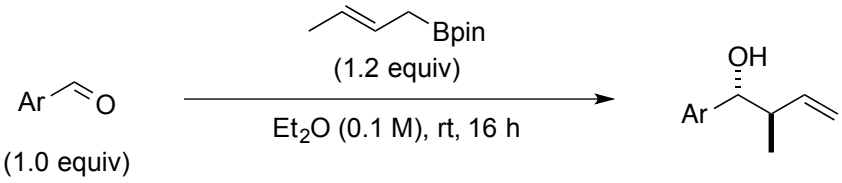
(1.0 equiv) (1.1 equiv)



$C_{10}H_{12}O$
MW: 148.09

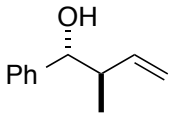
A one-neck, 100 mL round-bottom flask equipped with a condenser was charged with styrene oxide (1.14 mL, 10.0 mmol, 1.0 equiv) and THF (6.0 mL, 1.5 M) under a positive pressure of argon atm. Vinyl magnesium bromide (11.0 mL, 11.0 mmol, 1.1 equiv) was added dropwise at rt and the contents were stirred for 30 minutes at this temperature and then heated under reflux for 2 h, cooled to rt, quenched with ice (ca. 2 g), and the resulting suspension was dissolved with a 2 M aq. HCl (10 mL). The ethereal phase was separated and washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 9:1) to afford **SI-7** as a clear oil (622 mg, 4.2 mmol, 42%). Spectral and physical data were in accordance with the literature.[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 6.02 (ddd, *J* = 17.1, 10.5, 7.7 Hz, 1H), 5.24 – 5.16 (m, 2H), 3.83 (dd, *J* = 7.1, 0.8 Hz, 2H), 3.54 (app q, *J* = 7.2 Hz, 1H), 1.53 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 138.4, 128.9, 128.1, 127.1, 117.3, 66.2, 52.7.

2.9 General procedure 3 (GP3): Diastereoselective crotylation to furnish SI-8 and SI-9



To a one-neck, 50 mL round-bottom flask containing a solution of trans-crotylboronic acid pinacol ester (1.2 equiv) in Et_2O (0.1 M) was added a solution of the corresponding aldehyde (1.0 equiv) in Et_2O (2 mL) and the contents were stirred at rt for 16 h. The reaction mixture was quenched with 1.0 M aq. NaOH (2 mL/mmol) and 30% aq. H_2O_2 (2 mL/mmol) and stirred at rt for 1 h. The contents were partitioned between Et_2O (10 mL) and water (10 mL), and the ethereal phase was washed with water (10 mL), sat. aq. NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

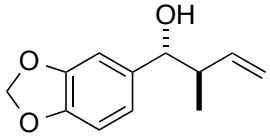
2-Methyl-1-phenylbut-3-en-1-ol (SI-8)



98:2 dr
$C_{11}H_{14}O$
MW: 162.10

From benzaldehyde (203 µL, 2.0 mmol) following **GP3**. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 95:5) to afford **SI-8** as a mixture of diastereomers in a 98:2 ratio*, as a colorless oil (300 mg, 1.85 mmol, 93%). Spectral and physical data were in accordance with the literature.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 5.82 (ddd, J = 17.2, 10.3, 8.2 Hz, 1H), 5.22 (ddd, J = 9.1, 1.8, 0.9 Hz, 1H), 5.18 – 5.16 (m, 1H), 4.36 (dd, J = 7.8, 2.6 Hz, 1H), 2.49 (dq, J = 14.7, 7.6, 1H), 2.20 (d, J = 2.7 Hz, 1H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 140.8, 128.4, 127.8, 127.0, 116.9, 78.0, 46.4, 16.6. *Determined by GC analysis on the crude residue.

1-(1,3-Benzodioxol-5-yl)-2-methyl-but-3-en-1-ol (SI-9)



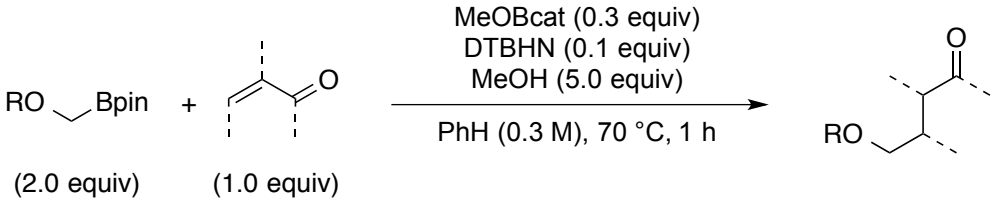
99:1 dr
$C_{12}H_{14}O_3$
MW: 206.09

From piperonal (1.38 g, 9.2 mmol) following **GP3**. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 95:5) to afford **SI-9** as a mixture of diastereomers in a 99:1 ratio*, as a colorless oil (692 mg, 3.4 mmol, 37%). Spectral and physical data were in accordance with the literature.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.77 (d, J = 1.0 Hz, 2H), 5.95 (s, 2H), 5.80 (ddd, J = 17.2, 10.3, 8.3 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.26 (d, J = 8.1 Hz, 1H), 2.41 (sep, J = 7.0 Hz, 1H), 2.11 (bs, 1H),

0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.2, 140.9, 136.6, 120.6, 117.0, 108.0, 107.2, 101.1, 77.9, 46.6, 16.7. *Determined by GC analysis on the crude residue.

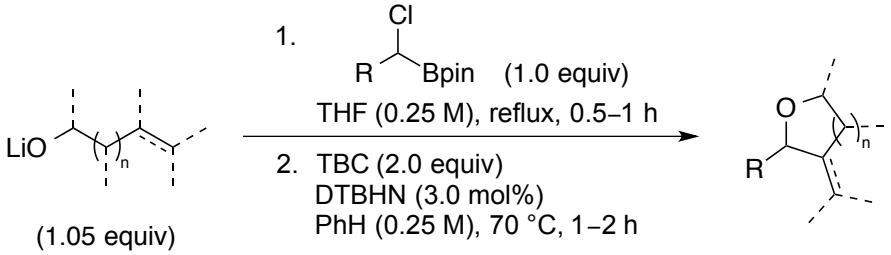
3. General Experimental Procedures for the Deboronative Radical Chain Reactions

3.1 General procedure 4 (GP4): Hydroalkoxymethylation of enones



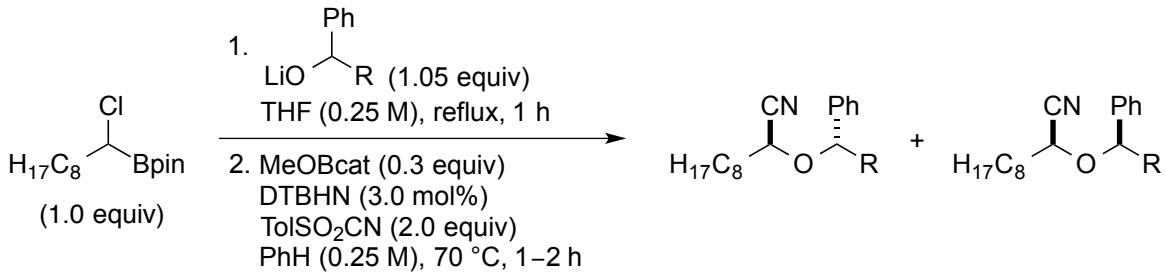
A two-necks, 25 mL round-bottom flask equipped with a condenser was charged with 1-alkoxymethyl pinacol boronic ester (2.0 equiv), PhH (0.3 M), MeOBcat (1.0 M in benzene, 0.3 equiv), the corresponding enone (1.0 equiv), MeOH (5.0 equiv) and DTBHN (0.1 equiv) under a positive pressure of N_2 atm. The reaction mixture was heated to 70 °C and stirred for 1 h, then partitioned at rt between TBME (20 mL) and 1 M aq. HCl (20 mL). The phases were separated and the aqueous phase was back-extracted with TBME (2×5 mL). The combined ethereal phases were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

3.2 General procedure 5 (GP5): 1,2-Metalate shift/reductive radical cyclization sequence



A two-necks, 25 mL round-bottom flask was charged with the corresponding alcohol (1.05 equiv) and THF (0.35 M). Then *n*-butyllithium (1.05 equiv, 2.35 M in *n*-hexane) was added dropwise at 0 °C and the reaction mixture was stirred at this temperature for 30 minutes. A solution of 1-chloro pinacol boronic ester (1.0 equiv) in THF (1.0 M) was added dropwise and the contents were heated under reflux for 0.5–1 h. The reaction mixture was cooled to rt and the solvent was removed *in vacuo* (Schleck line). The residue was dissolved in PhH (0.25 M) and TBC (2.0 equiv) and DTBHN (3.0 mol%) were added in sequence under a positive pressure of N_2 atm. The contents were heated at 70 °C for 1–2 h, cooled to rt, quenched with 2 M aq. NaOH (2 mL/mmol), 30% aq. H_2O_2 (2 mL/mmol), and partitioned between water (20 mL) and Et_2O (20 mL). The two phases were separated and the aqueous phase was back-extracted with Et_2O (2×5 mL). The collected ethereal phase was washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered over a short pad of silica and concentrated *in vacuo*. The relative stereochemistry of the cyclized products was determined in accordance with the literature.[19,20] The preponderance of the *cis* isomer over the *trans* isomer can be rationalized via the transition state model proposed by Beckwith and Houk.[21,22]

3.3 General procedure 6 (GP6): 1,2-Metalate shift/radical deboronative cyanation sequence



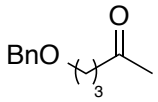
A two-necks, 25 mL round-bottom flask was charged with the corresponding alcohol (1.05 equiv) and THF (0.35 M). Then *n*-butyllithium (1.05 equiv, 2.35 M in hexane) was added dropwise at 0 °C and the reaction mixture was stirred at this temperature for 30 minutes. A solution of **4a** (289 mg, 1.0 mmol, 1.0 equiv) in THF (1.0 M) was added dropwise and the contents were heated under reflux for 1 h. The reaction mixture was cooled to rt and the solvent was removed *in vacuo* (Schleck line). The residue was dissolved in PhH (4 mL, 0.25 M) and *p*-toluenesulfonyl cyanide (362 mg, 2.0 equiv), MeOBcat (0.3 mL, 0.3 mmol, 1 M in PhH) and DTBHN (5 mg, 3.0 mol%) were added in sequence under a positive pressure of N_2 atm. The

contents were heated at 70 °C for 1–2 h, cooled to rt, quenched with 2 M aq. NaOH (2 mL/mmol), 30% aq. H_2O_2 (2 mL/mmol), and partitioned between water (20 mL) and TBME (20 mL). The two phases were separated and the aqueous phase was back-extracted with TBME (2×5 mL). The collected ethereal phase was washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*.

4. Descriptions of Isolations and Characterizations of Deboronative Radical Chain Reaction Products

4.1 Hydroalkoxymethylation of enones to furnish 3a–i, 3ba and 3ea

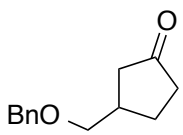
5-(Benzyloxy)pentan-2-one (3a)



$C_{12}H_{16}O_2$
MW: 192.12

From but-3-en-2-one (80 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 9:1) to afford **3a** as a yellow oil (97 mg, 0.51 mmol, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 4.48 (s, 2H), 3.48 (t, J = 6.1 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.13 (s, 3H), 1.89 (ddd, J = 13.4, 7.1, 6.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 138.5, 128.5, 127.8, 127.7, 73.0, 69.4, 40.5, 30.1, 24.0. IR (neat): 2930, 2856, 1712, 1360, 1164, 1088, 1027, 969 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{16}O_2Na$ $[M+Na]^+$: 215.1043; found: 215.1047.

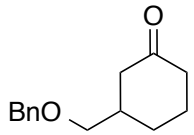
3-((Benzyloxy)methyl)cyclopentan-1-one (3b)



$C_{13}H_{16}O_2$
MW: 204.12

From cyclopent-2-en-1-one (84 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3b** as a yellow oil (166 mg, 0.81 mmol, 81%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.52 (s, 2H), 3.48 (d, J = 6.0 Hz, 2H), 2.61 – 2.46 (m, 1H), 2.44 – 2.09 (m, 4H), 2.03 (ddd, J = 18.3, 8.6, 1.1 Hz, 1H), 1.84 – 1.65 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.3, 138.3, 128.5, 127.8, 127.6, 73.4, 73.3, 42.2, 38.0, 37.0, 26.2. IR (neat): 2929, 2856, 1735, 1454, 1402, 1156, 1094, 1078 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{16}O_2Na$ $[M+Na]^+$: 227.1043; found: 227.1049.

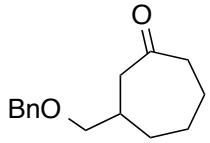
3-((Benzyloxy)methyl)cyclohexan-1-one (3c)



$C_{14}H_{18}O_2$
MW: 218.13

From cyclohex-2-en-1-one (97 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3c** as a yellow oil (146 mg, 0.67 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 4.50 (s, 2H), 3.37 (d, *J* = 5.4 Hz, 2H), 2.50 – 2.41 (m, 1H), 2.40 – 2.31 (m, 1H), 2.31 – 2.00 (m, 4H), 1.98 – 1.90 (m, 1H), 1.66 (dtdd, *J* = 12.7, 11.7, 4.8, 3.2 Hz, 1H), 1.56 – 1.40 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 138.4, 128.4, 127.7, 127.6, 74.3, 73.1, 44.9, 41.5, 39.3, 28.2, 25.0. IR (neat): 2925, 2853, 1707, 1452, 1362, 1223, 1096, 1074, 1052 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1380; found: 219.1386.

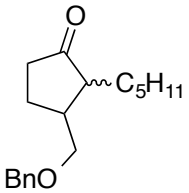
3-((Benzyloxy)methyl)cycloheptan-1-one (3d)



$C_{15}H_{20}O_2$
MW: 232.15

From cyclohept-2-en-1-one (139 µL, 80% technical grade, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3d** as a colorless oil (148 mg, 0.64 mmol, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.49 (s, 2H), 3.41 – 3.19 (m, 2H), 2.60 (ddd, *J* = 14.9, 2.6, 1.3 Hz, 1H), 2.48 (dd, *J* = 7.8, 4.5 Hz, 2H), 2.38 (dd, *J* = 14.9, 11.2 Hz, 1H), 2.08 – 1.80 (m, 4H), 1.67 – 1.13 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 138.4, 128.4, 127.7, 127.6, 75.1, 73.1, 47.1, 44.0, 36.5, 33.6, 28.8, 24.6. IR (neat): 2924, 2854, 1698, 1454, 1339, 1098, 911, 730, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{20}O_2Na$ $[M+Na]^+$: 255.1356; found: 255.1350.

3-((Benzyloxy)methyl)-2-pentylcyclopentan-1-one (3e)

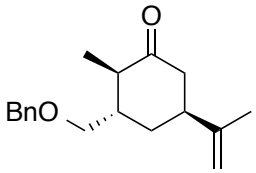


3:1 dr
$C_{18}H_{26}O_2$
MW: 274.19

From 2-pentylcyclopent-2-en-1-one (165 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3e** as a mixture of diastereomers in a 3:1 ratio*, as a yellow oil (232 mg, 0.85 mmol, 85%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.63 – 4.47 (m, 2H), 3.59 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.48 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.41 – 2.27 (m, 1H), 2.25 – 2.07 (m, 3H), 2.01 – 1.91 (m, 1H), 1.79 – 1.15 (m, 9H), 0.87 (app t, *J* = 6.8 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.0, 138.5,

128.5, 127.7, 127.6, 73.3, 72.9, 51.6, 42.1, 37.8, 32.1, 28.8, 26.7, 24.6, 22.6, 14.2. IR (neat): 2954, 2926, 2856, 1735, 1701, 1454, 1364, 1100, 1027 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{26}O_2Na$ $[M+Na]^+$: 297.1825; found: 297.1829. *Determined by GC analysis on the crude residue.

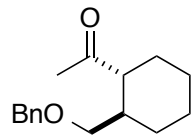
(5*S*)-3-((Benzyloxy)methyl)-2-methyl-5-(prop-1-en-2-yl)cyclohexan-1-one (3f)



6:4:3 dr
$C_{18}H_{24}O_2$
MW: 272.18

From D-carvone (160 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 9:1) to afford **3f** as a mixture of diastereomers in a 6:4:3 ratio*, as a clear oil (238 mg, 0.87 mmol, 87%). *Mixture of the two majors diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 9H), 4.78 – 4.74 (m, 1H), 4.72 – 4.69 (m, 0.5H), 4.66 – 4.64 (m, 0.5H), 4.63 – 4.60 (m, 1H), 4.50 – 4.31 (m, 3H), 3.45 – 3.30 (m, 2.5H), 3.23 (dd, *J* = 9.4, 8.4 Hz, 0.5H), 2.66 – 2.50 (m, 2.5H), 2.47 (d, *J* = 6.1 Hz, 0.5H), 2.44 – 2.26 (m, 3H), 2.18 (ddd, *J* = 13.5, 12.4, 1.1 Hz, 0.5H), 2.14 – 2.03 (m, 0.5H), 1.95 – 1.87 (m, 2H), 1.84 – 1.74 (m, 1H), 1.66 (s, 5H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 1.5H). *Minor diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 4.78 – 4.72 (m, 2H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 3.57 – 3.46 (m, 2H), 2.49 – 2.38 (m, 2H), 2.37 – 2.21 (m, 2H), 2.03 (dq, *J* = 12.8, 2.9, 2.5 Hz, 1H), 1.81 – 1.70 (m, 4H), 1.69 – 1.56 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H). *Mixture of the two majors diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 212.3, 147.8, 147.0, 138.5, 138.3, 128.51, 128.49, 127.74, 127.70, 127.64, 127.61, 111.7, 109.9, 73.3, 72.4, 69.1, 46.40, 46.36, 46.3, 44.0, 41.3, 40.6, 33.2, 30.2, 21.8, 20.8, 13.5, 11.9. *Minor diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7, 147.7, 138.5, 128.6, 127.83, 127.77, 109.9, 73.5, 72.3, 46.7, 46.2, 45.2, 45.1, 35.0, 20.6, 11.5. IR (neat): 2859, 1707, 1453, 1097, 893, 735, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849; found: 273.1847. *Determined by ^{1}H NMR analysis on the crude residue.

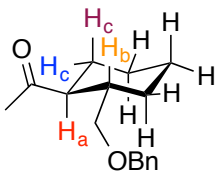
1-(2-((Benzyloxy)methyl)cyclohexyl)ethan-1-one (3g)



6:1 dr
$C_{16}H_{22}O_2$
MW: 246.16

From 1-(cyclohex-1-en-1-yl)ethan-1-one (129 µL, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/ TBME 9:1) to afford **3g** as a mixture of diastereomers in a 6:1 ratio*, as a yellow oil (108 mg, 0.44 mmol, 44%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 4.42 – 4.40 (m, 2H), 3.34 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.24 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.32 (ddd, *J* = 11.2, 8.8, 3.3 Hz, 1H), 2.09 (s, 3H), 1.98 (ttd, *J* = 10.9, 5.5, 3.6 Hz, 1H), 1.87 – 1.69 (m, 3H), 1.37 – 1.08 (m, 5H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 138.6, 128.4, 127.7, 127.6, 74.4, 73.2, 54.9, 39.4, 29.6, 29.1, 28.9, 25.7, 25.5. IR (neat): 2924, 2853, 1703, 1450, 1361, 1167, 1103, 1074 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{23}O_2$ $[M+H]^+$: 247.1693; found: 247.1689. *Determined by GC analysis on the crude residue.

Determination of the relative stereochemistry of the *trans* isomer by ^{1}H NMR coupling constants:

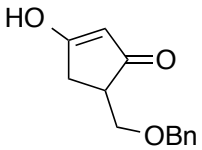


^{1}H NMR: 2.32 ppm
(ddd, *J* = 11.2, 8.8, 3.3 Hz, 1Ha)

$^3J_{Ha\text{-}Hc(ax)}$ and $^3J_{Ha\text{-}Hb}$

$^3J_{Ha\text{-}Hc(eq)}$

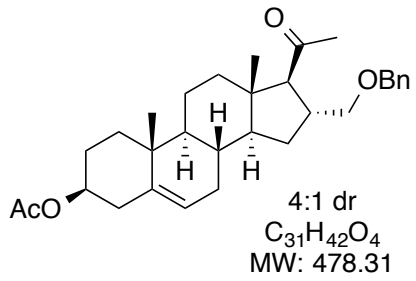
5-((Benzyloxy)methyl)-3-hydroxycyclopent-2-en-1-one (3h)



$C_{13}H_{14}O_3$
MW: 218.09

From 4-cyclopentene-1,3-dione (96 mg, 1.0 mmol) and **2a** (496 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (heptanes/TBME 4:6) to afford **3h** as a white powder (150 mg, 0.69 mmol, 69%). A sample was crystallized by solvent vapor exchange (Et_2O/*n*-pentane) to furnish colorless crystals. The molecular structure of the isomer was determined by X-ray crystallography (see 6. X-Ray structure of 5-((benzyloxy)methyl)-3-hydroxycyclopent-2-en 1-one). m.p. = 95.8 – 96.4 °C (Et_2O/*n*-pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.33 – 7.11 (m, 5H), 5.35 (s, 1H), 4.46 (s, 2H), 3.61 (qd, *J* = 9.0, 5.8 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.60 (dd, *J* = 18.3, 6.8 Hz, 1H), 2.41 (dd, *J* = 18.3, 2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 201.1, 137.5, 128.7, 128.1, 127.9, 106.5, 73.6, 69.86, 43.3, 35.8. IR (neat): 2858, 1941, 1576, 1450, 1413, 1252, 1169, 1090, 1038, 917, 838, 698, 615 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1016; found: 219.1014.

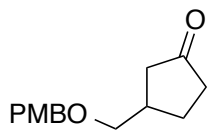
(3*S*,8*S*,9*S*,10*R*,13*S*,14*S*)-17-Acetyl-16-((benzyloxy)methyl)-10,13-dimethyl-2,3,4,7,8,9,10, 11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl acetate (3i)



4:1 dr
$C_{31}H_{42}O_4$
MW: 478.31

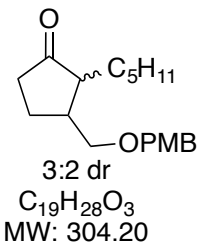
From 16-dehydropregnenolone acetate (356 mg, 1.0 mmol) and **2a** (744 mg, 3.0 mmol) following **GP4**. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 95:5) followed by crystallization from Et_2O to afford **3i** as a mixture of diastereomers in a 4:1 ratio*, as a white powder (368 mg, 0.77 mmol, 77%). *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 – 7.17 (m, 5H), 5.30 (d, *J* = 4.4 Hz, 1H), 4.59 – 4.46 (m, 1H), 4.38 (q, *J* = 12.1 Hz, 2H), 3.29 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.18 (app t, *J* = 8.3 Hz, 1H), 2.89 (dq, *J* = 14.4, 7.4 Hz, 1H), 2.32 (d, *J* = 8.6 Hz, 1H), 2.27 – 2.22 (m, 2H), 2.04 (s, 3H), 1.96 (s, 3H), 1.94 – 1.85 (m, 2H), 1.81 – 1.77 (m, 2H), 1.59 – 1.44 (m, 3H), 1.44 – 1.31 (m, 4H), 1.20 – 1.15 (m, 2H), 1.11 – 1.04 (m, 1H), 0.98 – 0.90 (m, 4H [containing 0.94 (s, 3H)]), 0.61 (s, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 170.6, 139.8, 138.8, 128.4, 127.6, 127.5, 122.4, 74.4, 73.9, 72.8, 67.9, 55.6, 50.0, 45.1, 38.9, 38.2, 37.3, 37.1, 36.7, 32.1, 31.8, 28.7, 27.8, 24.7, 21.5, 21.1, 19.4, 14.2. IR (neat): 2936, 1725, 1702, 1366, 1244, 1038, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{31}H_{43}O_4$ $[M+H]^+$: 479.3156; found: 479.3150. *Determined by GC analysis on the crude residue.

3-(((4-Methoxybenzyl)oxy)methyl)cyclopentan-1-one (3ba)



$C_{14}H_{18}O_3$
MW: 234.13

From cyclopent-2-en-1-one (84 µL, 1.0 mmol) and **2b** (556 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3ba** as a yellow oil (189 mg, 0.81 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 6.89 – 6.86 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.35 (d, *J* = 5.4 Hz, 2H), 2.45 – 2.08 (m, 4H + 2H[§]), 2.07 – 1.92 (m, 1H), 1.66 (dtdd, *J* = 12.8, 11.7, 4.8, 3.3 Hz, 1H), 1.49 – 1.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 159.3, 130.5[§], 129.2, 113.9, 74.0, 72.9, 55.4, 45.0, 41.6, 39.4, 28.3, 25.1. IR (neat): 2932, 2853, 1707, 1611, 1510, 1449, 1243, 1172, 1093, 1031 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.1148; found: 257.1143. [§]Contaminated with an undetermined product.

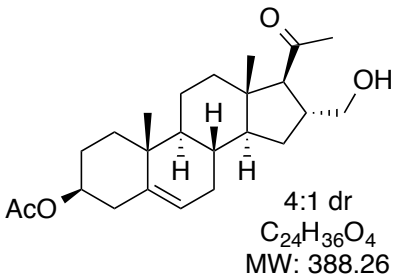


3-(((4-Methoxybenzyl)oxy)methyl)-2-pentylcyclopentan-1-one (3ea)

From 2-pentylcyclopent-2-en-1-one (165 µL, 1.0 mmol) and **2b** (556 mg, 2.0 mmol) following **GP4**. The crude residue was purified by FCC on neutral aluminium oxide (*n*-pentane/TBME 8:2) to afford **3ea** as a mixture of diastereomers in a 3:2 ratio*, as a yellow oil (233 mg, 0.77 mmol, 77%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 6.90 – 6.85 (m, 2H), 4.53 – 4.40 (m, 2H), 3.81 (s, 3H), 3.56 (d, *J* = 9.2, 4.4 Hz, 1H), 3.44 (dd, *J* = 9.3, 6.0 Hz, 1H), 2.40 – 2.25 (m, 1H), 2.23 – 2.03 (m, 3H), 2.00 – 1.87 (m, 1H), 1.76 – 1.21 (m, 9H), 0.87 (app t, *J* = 6.8 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.1, 159.3, 130.6, 129.2, 113.9, 73.0, 72.6, 55.4, 51.6, 42.1, 37.7, 32.2, 28.8, 26.7, 24.6, 22.6, 14.2. IR (neat): 2928, 2856, 1733, 1611, 1511, 1456, 1245, 1171, 1091, 1032, 818 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{27}O_3$ $[M-H]^+$: 303.1955; found: 303.1952. *Determined by GC analysis on the crude residue.

4.2 Formal hydroxymethylation of 16-dehydropregnenolone acetate to furnish 3ia

(3*S*,8*S*,9*S*,10*R*,13*S*,14*S*)-17-Acetyl-16-(hydroxymethyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (3ia)

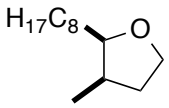


From 16-dehydropregnenolone acetate (356 mg, 1.0 mmol) and **2a** (744 mg, 3.0 mmol) following **GP4**. The crude residue was filtered through a short pad of silica gel (washed with heptanes/EtOAc 9:1) and the filtrate was concentrated *in vacuo*. The crude residue was then dissolved in a 10% formic acid in methanol (0.1 M) solution and 10% Pd/C was added. The contents were stirred at rt for 3 days, then filtered over a short pad of celite (washed with TBME) and the volatiles were removed *in vacuo*. The crude residue was purified by FCC on silica gel (heptanes/EtOAc 2:8) to afford **3ia** as a mixture of diastereomers in a 4:1 ratio*, as a white powder (173 mg, 0.44 mmol, 44%). m.p. = 166.8 – 168.5 °C. *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, *J* = 5.0 Hz, 1H), 4.67 – 4.53 (m, 1H), 3.60 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.34 (dd, *J* = 10.3, 8.2 Hz, 1H), 2.91 – 2.77 (m, 1H), 2.39 (d, *J* = 8.6 Hz, 1H), 2.36 – 2.27 (m, 2H), 2.16 (s, 3H), 2.03 (s, 3H), 2.01 – 1.92 (m,

2H), 1.90 – 1.81 (m, 2H), 1.68 – 1.35 (m, 5H), 1.28 – 1.21 (m, 5H [containing 1.24 (s, 3H)]), 1.15 (td, *J* = 13.9, 13.2, 4.0 Hz, 1H), 1.06 – 0.98 (m, 4H [containing 1.21 (s, 3H)]), 0.68 (s, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 170.7, 139.8, 122.3, 73.9, 68.3, 67.4, 55.7, 50.0, 45.0, 39.5, 39.0, 38.2, 37.1, 31.9, 31.84, 31.78, 28.2, 27.9, 25.0, 21.6, 21.1, 19.4, 14.2. IR (neat): 3393, 2938, 1731, 1683, 1365, 1246, 1034 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{37}O_4$ $[M+H]^+$: 389.2686; found: 389.2691. *Determined by ^{1}H NMR analysis on the crude residue.

4.3 1,2-Metalate shift/reductive radical cyclization sequence to furnish 5a–r

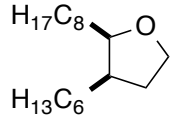
3-Methyl-2-octyl-tetrahydrofuran (5a)



87:13 dr
$C_{13}H_{26}O$
MW: 198.20

From **4a** (289 mg, 1.0 mmol) and but-3-en-1-ol (90 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5a** as a mixture of diastereomers in a 87:13 ratio*, as a colorless oil (137 mg, 0.69 mmol, 69%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (td, *J* = 8.0, 6.6 Hz, 1H), 3.71 (td, *J* = 8.4, 5.6 Hz, 1H), 2.28 – 2.12 (m, 1H), 2.07 (ddt, *J* = 12.2, 8.6, 6.9 Hz, 1H), 1.63 – 1.21 (m, 16H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.88 (app t, *J* = 6.9 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.8, 65.9, 35.3, 34.0, 31.9, 30.5, 29.9, 29.6, 29.3, 26.8, 22.7, 14.3, 14.1. IR (neat): 2956, 2924, 2854, 1458, 1098, 1008 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{25}O$ $[M-H]^+$: 197.1899; found: 197.1898. *Determined by GC analysis on the crude residue.

3-Hexyl-2-octyl-tetrahydrofuran (5b)

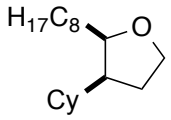


76:24 dr
$C_{18}H_{36}O$
MW: 268.28

From **4a** (289 mg, 1.0 mmol) and cis-3-nonen-1-ol (177 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5b** as a mixture of diastereomers in a 76:24 ratio*, as a colorless oil (180 mg, 0.67 mmol, 67%). *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (td, *J* = 8.2, 4.7 Hz, 1H), 3.82 – 3.76 (m, 1.6H), 3.72 (q, *J* = 7.7 Hz, 1H), 3.37 (td, *J* = 7.5, 3.3 Hz, 0.3H), 2.10 – 1.92 (m, 2.3H), 1.64 – 1.54 (m, 2H), 1.51 – 1.11 (m, 35H), 0.91 – 0.85 (m, 8.7H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.4, 66.1, 41.6, 31.92, 31.87, 31.2, 30.2, 29.9, 29.62, 29.58, 29.3, 28.7, 28.4, 26.7, 22.7, 14.12, 14.10. IR (neat): 2952, 2923, 2851, 1457, 1057, 720 cm^{-1}.

HRMS (ESI) calcd. for $C_{18}H_{35}O$ $[M-H]^+$: 267.2682; found: 267.2690. *Determined by GC analysis on the crude residue.

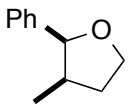
3-Cyclohexyl-2-octyl-tetrahydrofuran (5c)



59:41 dr
$C_{18}H_{34}O$
MW: 266.26

From **4a** (289 mg, 1.0 mmol) and 3-cyclohexylidenepropan-1-ol (147 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5c** as a mixture of diastereomers in a 59:41 ratio*, as a colorless oil (167 mg, 0.63 mmol, 63%). *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 – 3.91 (m, 1H *maj*), 3.86 (td, *J* = 9.0, 2.6 Hz, 1H *maj*), 3.79 – 3.67 (m, 1H *maj* + 2H *min*), 3.67 – 3.58 (m, 1H *min*), 1.99 – 1.82 (m, 2H *maj* + 2H *min*), 1.79 – 1.39 (m, 15H), 1.38 – 1.12 (m, 30H), 1.05 – 0.94 (m, 2H *maj* + 2H *min*), 0.88 (app t, *J* = 6.6 Hz, 3H *maj* + 3H *min*). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.2 (*min*), 79.8 (*maj*), 66.9 (*min*), 66.1 (*maj*), 50.4 (*min*), 49.0 (*maj*), 40.9 (*min*), 37.7 (*maj*), 36.3 (*min*), 32.8 (*maj*), 32.4 (*min*), 32.3 (*maj*), 31.9 (*maj* + *min*), 30.9 (*min*), 30.5 (*min*), 29.84 (*min*), 29.81 (*maj*), 29.72 (*maj*), 29.66 (*min*), 29.34 (*maj*), 29.33 (*min*), 28.9 (*maj*), 28.7 (*maj*), 26.7 (*min*), 26.59 (*min*), 26.55 (*maj*), 26.5 (*min*), 26.42 (*min*), 26.38 (*maj*), 26.3 (*maj*), 26.1 (*maj*), 22.7 (*maj* + *min*), 14.1 (*maj* + *min*). IR (neat): 2921, 2847, 1448, 1048, 891, 720 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{33}O$ $[M-H]^+$: 265.2526; found: 265.2526. *Determined by GC analysis on the crude residue.

3-Methyl-2-phenyltetrahydrofuran (5d)

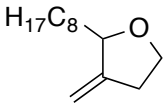


57:43 dr
$C_{11}H_{14}O$
MW: 162.10

From **4b** (252 mg, 1.0 mmol) and but-3-en-1-ol (82 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5d** as a as a mixture of diastereomers in a 57:43 ratio*, as a colorless oil (73 mg, 0.45 mmol, 45%).[§] Spectral and physical data were in accordance with the literature.[23,24] *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 10H), 4.95 (d, *J* = 6.4 Hz, 1H *maj*), 4.28 (d, *J* = 8.2 Hz, 1H *min*), 4.21 – 4.14 (m, 1H *maj*), 4.09 (td, *J* = 8.2, 6.8 Hz, 1H *min*), 4.02 (td, *J* = 8.4, 4.2 Hz, 1H *min*), 3.92 (td, *J* = 8.1, 6.9 Hz, 1H *maj*), 2.51 (sep, *J* = 6.9 Hz, 1H *maj*), 2.36 – 2.25 (m, 1H *min*), 2.25 – 2.13 (m, 1H *maj*), 2.11 – 1.99 (m, 1H *min*), 1.76 – 1.65 (m, 1H *maj* + 1H *min*), 1.07 (d, *J* = 6.5 Hz, 3H *min*), 0.60 (d, *J* = 7.0 Hz, 3H *maj*). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2 (*min*), 140.8 (*maj*), 128.3 (*min*), 127.9 (*maj*), 127.4 (*min*), 126.8 (*maj*), 126.3 (*maj*), 126.1 (*min*), 87.9 (*min*), 83.6 (*maj*), 67.9 (*min*), 67.3 (*maj*), 42.9 (*min*), 37.7

(*maj*), 35.0 (*min*), 33.7 (*maj*), 16.4 (*min*), 15.4 (*maj*). *Determined by GC analysis on the crude residue. §Contaminated with 15% of the reduced alkene.[25]

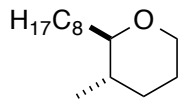
3-Methylene-2-octyl-tetrahydrofuran (5e)



$C_{13}H_{24}O$
MW: 196.18

From **4a** (289 mg, 1.0 mmol) and 3-butyn-1-ol (90 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **5e** as a colorless oil (88 mg, 0.45 mmol, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (q, *J* = 2.2 Hz, 1H), 4.84 (q, *J* = 2.2 Hz, 1H), 4.22 – 4.20 (m, 1H), 3.97 (dt, *J* = 8.4, 6.3 Hz, 1H), 3.73 (q, *J* = 7.9 Hz, 1H), 2.60 – 2.53 (m, 2H), 1.70 – 1.19 (m, 14H), 0.88 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 104.1, 80.6, 66.7, 35.1, 33.4, 31.9, 29.8, 29.6, 29.3, 25.7, 22.7, 14.1. IR (neat): 2923, 2852, 1665, 1465, 1433, 1090, 1067, 980, 882, 772 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{24}O$ $[M]^+$: 196.1822; found: 196.1824.

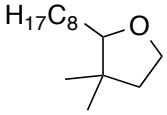
3-Methyl-2-octyltetrahydro-2*H*-pyran (5f)



75:25 dr
$C_{14}H_{28}O$
MW: 212.21

From **4a** (289 mg, 1.0 mmol) and 4-penten-1-ol (110 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5f** as a mixture of diastereomers in a 75:25 ratio*, as a colorless oil (84 mg, 0.40 mmol, 40%).§ *Mixture of major diastereomer and SI-11* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H **SI-10**), 5.09 – 4.71 (m, 2H **SI-10**), 4.02 – 3.81 (m, 1H **5f** *maj*), 3.38 (td, *J* = 6.6, 5.0 Hz, 4H **SI-10**), 3.30 (dd, *J* = 11.4, 2.4 Hz, 1H **5f** *maj*), 2.83 (td, *J* = 8.8, 2.3 Hz, 1H **5f** *maj*), 2.10 (q, *J* = 7.0 Hz, 2H **SI-10**), 1.79 – 1.43 (m, 6H **5f** *maj* + 4H **SI-10**), 1.39 – 1.19 (m, 12H **5f** *maj* + 12H **SI-10**), 1.11 (ddd, *J* = 24.3, 12.4, 4.2 Hz, 1H **5f** *maj*), 0.86 (app t, *J* = 7.0 Hz, 3H **5f** *maj* + 3H **SI-10**), 0.79 (d, *J* = 6.6 Hz, 3H **5f** *maj*). *Mixture of major diastereomer and SI-11* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (**SI-10**), 114.7 (**SI-10**), 83.8 (**5f** *maj*), 71.1 (**SI-10**), 70.2 (**SI-10**), 68.5 (**5f** *maj*), 35.5 (**5f** *maj*), 33.5 (**5f** *maj*), 33.0 (**5f** *maj*), 32.04 (**SI-10**), 32.02 (**5f** *maj*), 30.5 (**SI-10**), 30.1 (**5f** *maj*), 29.9 (**SI-10**), 29.8 (**5f** *maj*), 29.7 (**SI-10**), 29.6 (**SI-10**), 29.5 (**5f** *maj*), 29.4 (**SI-10**), 29.1 (**SI-10**), 26.9 (**5f** *maj*), 26.3 (**SI-10**), 25.5 (**5f** *maj*), 22.8 (**SI-10** + **5f** *maj*), 18.3 (**5f** *maj*), 14.2 (**SI-10** + **5f** *maj*). HRMS (ESI) calcd. for $C_{14}H_{28}O$ $[M]^+$: 212.2135; found: 211.2126. *Determined by GC analysis on the crude residue. §Yield estimated by GC analysis of the isolated mixture of **5f** and **SI-10** (see section By-products).

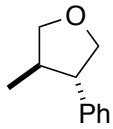
3,3-Dimethyl-2-octyl-tetrahydrofuran (5g)



$C_{14}H_{28}O$
MW: 212.21

From **4a** (289 mg, 1.0 mmol) and 3-methylbut-3-en-1-ol (109 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5g** as a colorless oil (113 mg, 0.53 mmol, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (p, *J* = 8.3 Hz, 1H), 3.76 (td, *J* = 8.5, 4.3 Hz, 1H), 3.28 (app t, *J* = 6.0 Hz, 1H), 1.78 – 1.66 (m, 2H), 1.65 – 1.50 (m, 1H), 1.37 – 1.23 (m, 13H), 1.02 (s, 3H), 0.89 (s, 3H), 0.88 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.3, 65.2, 41.5, 40.3, 31.9, 30.0, 29.6, 29.3, 27.6, 25.4, 22.7, 21.6, 14.1. IR (neat): 2953, 2924, 2854, 1465, 1367, 1098, 1025, 983, 904, 722 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{28}O$ $[M]^+$: 212.2135; found: 212.2114.

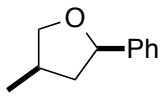
3-Methyl-4-phenyltetrahydrofuran (5h)



6:1 dr
$C_{11}H_{14}O$
MW: 162.1045

From **1** (194 µL, 1.0 mmol) and **SI-7** (156 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 7:3) to afford **5h** as a mixture of diastereomers in a 6:1 ratio*, as a light pink oil (76 mg, 0.47 mmol, 47%). Spectral and physical data were in accordance with the literature.[26] *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 7H), 4.20 (td, *J* = 8.0, 4.8 Hz, 2H *maj*), 4.15 – 4.10 (m, 0.18H *min*), 4.06 (dd, *J* = 8.1, 7.3 Hz, 0.18H *min*), 3.82 (t, *J* = 8.7 Hz, 1H *maj*), 3.52 (t, *J* = 8.0 Hz, 0.18H *min*), 3.48 (app t, *J* = 8.5 Hz, 1H *maj*), 3.43 – 3.28 (m, 0.31H), 2.88 (q, *J* = 8.8 Hz, 1H *maj*), 2.63 (dt, *J* = 14.4, 7.2 Hz, 0.18H), 2.47 – 2.25 (m, 1H *maj*), 1.03 (d, *J* = 6.6 Hz, 2H *maj*), 0.68 (d, *J* = 7.0 Hz, 0.38H). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 128.8, 127.8, 126.8, 75.8, 75.5, 53.9, 42.8, 15.7. *Determined by ^{1}H NMR analysis on the crude residue.

4-Methyl-2-phenyltetrahydrofuran (5i)

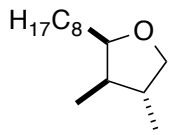


3:1 dr
$C_{11}H_{14}O$
MW: 162.1045

From **1** (194 µL, 1.0 mmol) and 1-phenylbut-3-en-1-ol (162 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5i** as a mixture of diastereomers in a 3:1 ratio*, as a light pink oil (84 mg, 0.52 mmol, 52%). *Mixture of diastereomers* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 5H), 7.17 (td, *J* = 6.3, 2.4 Hz, 1H), 4.95 (t, *J* = 6.9 Hz, 0.3H), 4.84 (dd, *J* = 9.8, 5.7 Hz, 1H), 4.15 (dd, *J* = 8.1, 7.0 Hz, 0.3H), 4.02 (t, *J* = 7.8 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 1H), 3.40 (dd, *J* = 8.1, 7.1 Hz, 0.3H), 2.49 – 2.28 (m, 2.4H), 1.99 – 1.81 (m, 0.6H), 1.44 – 1.31 (m, 1H), 1.02 (d, *J* = 6.3 Hz, 1.2H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.88 – 0.71 (m, 0.3H). *Mixture of diastereomers* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (*min*), 143.6

(*maj*), 128.44 (*maj*), 128.38 (*min*), 127.3 (*maj*), 127.1 (*min*), 125.8 (*maj*), 125.7 (*min*), 81.7 (*maj*), 80.2 (*min*), 75.8 (*min*), 75.6 (*maj*), 44.1 (*maj*), 42.8 (*min*), 35.1 (*maj*), 33.4 (*min*), 17.9 (*min*), 17.5 (*maj*). IR (neat): 2958, 2871, 1452, 1041, 1000, 752, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{13}O$ $[M-H]^+$: 161.0961; found: 161.0959. *Determined by ^1H NMR analysis on the crude residue.

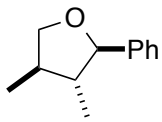
3,4-Dimethyl-2-octyl-tetrahydrofuran (5j)



73:17:9:1 dr
$C_{14}H_{28}O$
MW: 212.21

From **4a** (289 mg, 1.0 mmol) and 2-methylbut-3-en-1-ol (111 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5j** as a mixture of diastereomers in a 73:17:9:1 ratio*, as a colorless oil (147 mg, 0.69 mmol, 69%). *Major diastereomer* - ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 8.2, 7.3 Hz, 1H), 3.90 – 3.83 (m, 1H), 3.24 (dd, *J* = 8.2, 7.4 Hz, 1H), 1.84 (sext, *J* = 6.9 Hz, 1H), 1.75 (sext, *J* = 6.9 Hz, 1H), 1.51 – 1.23 (m, 14H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.86 (app t, *J* = 7.0 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.3, 73.8, 43.6, 40.8, 31.9, 31.0, 29.9, 29.7, 29.3, 26.7, 22.7, 17.2, 14.1, 13.6. IR (neat): 2956, 2923, 2853, 1456, 1377, 1105, 1036, 958, 935 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{28}O$ $[M]^+$: 212.2135; found: 212.2114. *Determined by GC analysis on the crude residue.

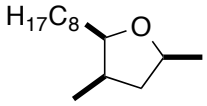
3,4-Dimethyl-2-phenyltetrahydrofuran (5k)



92:8 dr
$C_{12}H_{16}O$
MW: 176.12

From **1** (180 µL, 0.92 mmol) and **SI-7** (157 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5k** as a mixture of diastereomers in a 92:8 ratio*, as a light pink oil (98 mg, 0.56 mmol, 61%). *Mixture of diastereomers* - ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 4H), 7.24 – 7.14 (m, 1H), 4.37 (d, *J* = 7.9 Hz, 0.08H), 4.28 (d, *J* = 9.4 Hz, 1H), 4.18 (dd, *J* = 8.3, 6.4 Hz, 0.08H), 4.09 (t, *J* = 7.9 Hz, 1H), 3.57 (dd, *J* = 9.4, 8.2 Hz, 1.2H), 2.32 (ddd, *J* = 13.8, 6.9, 4.8 Hz, 0.08H), 2.11 – 1.97 (m, 0.08H), 1.98 – 1.85 (m, 1H), 1.47 (tq, *J* = 9.8, 6.5 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 3.4H), 0.93 (d, *J* = 6.5 Hz, 3.8H), 0.91 (d, *J* = 7.0 Hz, 0.4H), 0.83 – 0.77 (m, 0.2H). *Mixture of diastereomers* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (*min*), 142.5 (*maj*), 128.42 (*maj*), 128.37 (*min*), 127.6 (*maj*), 127.4 (*min*), 126.3 (*maj*), 126.1 (*min*), 88.8 (*maj*), 86.7 (*min*), 75.5 (*min*), 75.4 (*maj*), 50.8 (*maj*), 45.7 (*min*), 42.4 (*maj*), 37.0 (*min*), 15.2 (*maj*), 14.1 (*maj*), 13.5 (*min*), 12.1 (*min*). IR (neat): 2956, 2871, 1452, 1103, 1025, 963, 750, 697, 530 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found: 177.1272. *Determined by GC analysis on the crude residue.

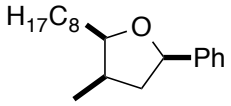
3,5-Dimethyl-2-octyl-tetrahydrofuran (5l)



84:16 dr
$C_{14}H_{28}O$
MW: 212.21

From **4a** (289 mg, 1.0 mmol) and pent-4-en-2-ol (108 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5l** as a mixture of diastereomers in a 84:16 ratio*[§], as a colorless oil (145 mg, 0.68 mmol, 68%). *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 – 3.82 (m, 1H), 3.72 – 3.67 (m, 1H), 2.29 – 2.15 (m, 2H), 1.51 – 1.37 (m, 3H), 1.35 – 1.23 (m, 14H), 1.15 – 1.05 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (app t, *J* = 6.8 Hz, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 81.9, 74.0, 42.0, 36.0, 31.9, 31.0, 30.0, 29.6, 29.3, 26.8, 22.7, 22.2, 15.8, 14.1. IR (neat): 2957, 2923, 2854, 1457, 1377, 1097, 940, 722 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{28}O$ $[M]^+$: 212.2135; found: 212.2110. *Determined by GC analysis on the crude residue. [§]for the two major diastereomers.

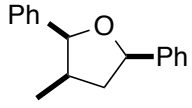
3-Methyl-2-octyl-5-phenyl-tetrahydrofuran (5m)



86:13:1 dr
$C_{19}H_{30}O$
MW: 274.23

From **4a** (289 mg, 1.0 mmol) and 1-phenylbut-3-en-1-ol (162 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5m** as a mixture of diastereomers in a 86:13:1 ratio*, as a colorless oil (182 mg, 0.66 mmol, 66%). *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.24 – 7.20 (m, 1H), 4.83 (dd, *J* = 8.7, 6.7 Hz, 1H), 3.95 (ddd, *J* = 8.6, 6.5, 4.7 Hz, 1H), 2.51 – 2.38 (m, 2H), 1.62 – 1.42 (m, 4H), 1.36 – 1.24 (m, 12H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.88 (app t, *J* = 6.8 Hz, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 128.2, 127.0, 125.8, 82.2, 79.9, 43.1, 36.4, 31.9, 31.1, 29.9, 29.6, 29.3, 26.7, 22.7, 15.2, 14.1. IR (neat): 2923, 2853, 1718, 1449, 1271, 1108, 1013, 760, 711, 698 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{31}O$ $[M+H]^+$: 275.2369; found: 275.2360. *Determined by GC analysis on the crude residue.

3-Methyl-2,5-diphenyltetrahydrofuran (5n)

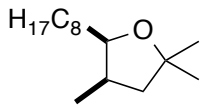


62:38 dr
$C_{17}H_{18}O$
MW: 238.14

From **4b** (252 mg, 1.0 mmol) and 1-phenylbut-3-en-1-ol (162 µL, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5n** as a mixture of diastereomers in a 62:38 ratio*, as a yellow oil (136 mg, 0.57 mmol, 57%).[§] *Mixture of diastereomers* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 4.8H *maj* + *min*), 7.42 – 7.26 (m, 13H *maj* + *min*), 5.16 (d, *J* = 7.4 Hz, 1H *maj*), 5.13 (dd, *J* = 7.7, 5.3 Hz, 0.6H *min*), 5.04 (dd, *J* = 9.1, 6.6 Hz, 1H *maj*), 4.46 (d, *J* = 7.4 Hz, 0.6H *min*), 2.74 (sep, *J* = 7.1 Hz, 1H

maj), 2.59 (ddd, *J* = 12.3, 7.3, 6.7 Hz, 1H *maj*), 2.31 – 2.19 (m, 1.2H *min*), 2.13 (dd, *J* = 8.0, 3.8 Hz, 0.6H *min*), 1.66 (ddd, *J* = 12.3, 9.1, 7.6 Hz, 1H *maj*), 1.12 (d, *J* = 6.1 Hz, 2H *min*), 0.63 (d, *J* = 7.0 Hz, 3H *maj*). *Mixture of diastereomers* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (*min*), 142.8 (*maj*), 141.4 (*min*), 140.7 (*maj*), 128.5 (*maj* + *min*), 128.1 (*maj*), 127.8 (*min*), 127.33 (*min*), 127.30 (*min*), 127.1 (*maj*), 126.8 (*maj*), 126.6 (*min*), 126.1 (*min*), 126.0 (*maj*), 89.0 (*min*), 84.1 (*maj*), 80.1 (*maj*), 79.6 (*min*), 43.1 (*min*), 42.5 (*maj*), 42.1 (*min*), 38.3 (*maj*), 17.0 (*maj*), 16.9 (*min*). IR (neat): 3029, 2959, 1495, 1450, 1095, 1024, 1005, 908, 743, 696 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{19}O$ $[M+H]^+$: 239.1430; found: 239.1427. *Determined by GC analysis on the crude residue. §Contaminated with 7% of benzaldehyde.

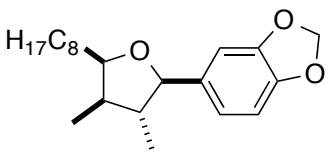
2,2,4-Trimethyl-5-octyl-tetrahydrofuran (5o)



86:14 dr
$C_{15}H_{30}O$
MW: 226.23

From **4a** (289 mg, 1.0 mmol) and 2-methylpent-4-en-2-ol (107 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5o** as a mixture of diastereomers in a 86:14 ratio*, as a colorless oil (107 mg, 0.47 mmol, 47%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (dt, *J* = 7.8, 5.8 Hz, 1H), 2.31 (sep, *J* = 7.0, 6.9 Hz, 1H), 1.91 (dd, *J* = 12.4, 7.6 Hz, 1H), 1.45 (dd, *J* = 12.4, 6.2 Hz, 2H), 1.30 – 1.21 (m, 16H), 1.19 (s, 3H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.88 (app t, *J* = 6.8 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.7, 78.9, 46.8, 36.4, 31.9, 30.9, 30.7, 30.0, 29.6, 29.3, 29.0, 26.5, 22.7, 14.8, 14.1. IR (neat): 2961, 2924, 2854, 1457, 1377, 1363, 1141, 1099, 998, 935 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{29}O$ $[M-H]^+$: 225.2213; found: 225.2214. *Determined by GC analysis on the crude residue.

5-(3,4-Dimethyl-5-octyltetrahydrofuran-2-yl)benzo[*d*][1,3]dioxole (5p)

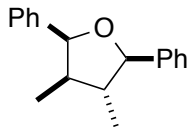


96:4 dr
$C_{21}H_{32}O_3$
MW: 332.24

From **4a** (289 mg, 1.0 mmol) and **SI-8** (216 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5p** as a mixture of diastereomers in a 96:4 ratio*, as a colorless oil (209 mg, 0.63 mmol, 63%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 – 6.84 (m, 1H), 6.79 – 6.73 (m, 2H), 5.93 (s, 2H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.03 (td, *J* = 8.3, 4.5 Hz, 1H), 1.98 (tq, *J* = 9.2, 7.1 Hz, 1H), 1.60 – 1.45 (m, 4H), 1.40 – 1.23 (m, 11H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.88 (app t, *J* = 7.0 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.0, 136.4, 120.1, 108.0, 106.9, 101.0, 87.9, 81.2, 49.3, 44.3, 32.13, 32.06, 30.0, 29.8, 29.5, 26.6, 22.8, 15.0, 14.3, 13.5.

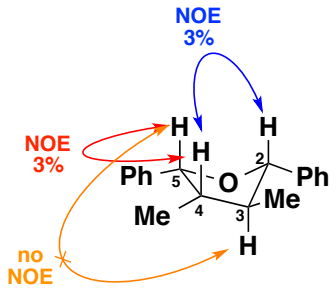
IR (neat): 2923, 2854, 1488, 1442, 1247, 1038, 936, 804 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{33}O_3$ $[M+H]^+$: 333.2424; found: 333.2419. *Determined by GC analysis on the crude residue.

3,4-Dimethyl-2,5-diphenyltetrahydrofuran (5q)

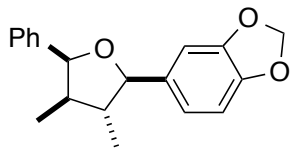


94:6 dr
$C_{18}H_{20}O$
MW: 252.15

From **4b** (360 mg, 1.43 mmol) and **SI-7** (217 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **5q** as a mixture of diastereomers in a 94:6 ratio*, as a yellow oil (141 mg, 0.56 mmol, 39%). *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.48 – 7.27 (m, 8H), 5.20 (d, *J* = 8.6 Hz, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 2.29 (tq, *J* = 8.7, 7.1 Hz, 1H), 1.80 (tq, *J* = 9.0, 6.6 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 128.4, 128.0, 127.6, 127.1, 127.0, 126.5, 87.6, 83.1, 48.9, 46.0, 15.4, 15.2. IR (neat): 3028, 2957, 1495, 1452, 1039, 1023, 998, 742, 696 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{21}O$ $[M+H]^+$: 253.1587; found: 253.1597. *Determined by GC analysis on the crude residue.



3,4-Dimethyl-5-phenyltetrahydrofuran-2-yl)benzo[*d*][1,3]dioxole (5r)

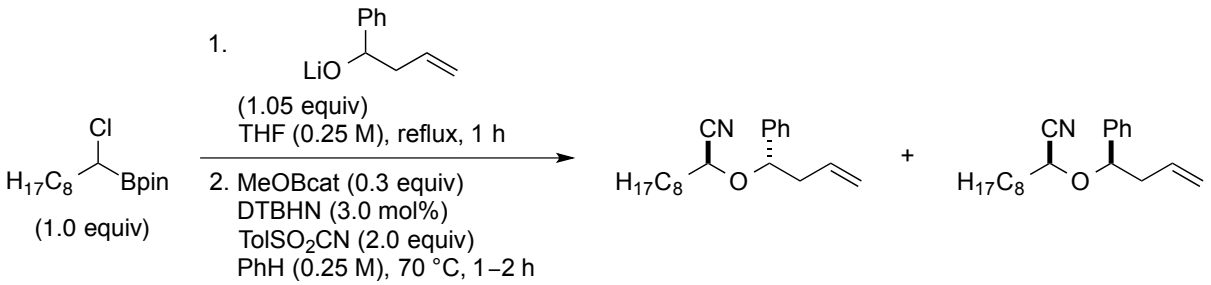


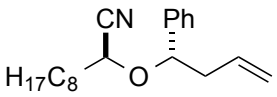
92:8 dr
$C_{19}H_{20}O_3$
MW: 296.14

From **4b** (252 mg, 1.0 mmol) and **SI-8** (216 mg, 1.05 mmol) following **GP5**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 8:2) to afford **5r** as a mixture of diastereomers in a 92:8 ratio*, as a yellow oil (191 mg, 0.65 mmol, 65%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.25 (m, 5H), 7.06 (d, *J* = 1.6 Hz, 1H), 6.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 4.37 (d, *J* = 9.2 Hz, 1H), 2.36 – 2.20 (m, 1H), 1.81 – 1.68 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.2, 141.0, 134.9, 128.5, 128.1, 127.6, 127.2, 127.1, 126.4, 120.3, 108.2, 107.1, 101.1, 87.6, 83.1, 48.9, 46.0, 15.5, 15.2. IR (neat): 2970, 2870, 1488, 1442, 1246, 1114, 1036, 935, 807, 748, 699 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{21}O_3$ $[M+H]^+$: 297.1485; found: 297.1479. *Determined by GC analysis on the crude residue.

4.4 1,2-Metalate shift/radical deboronative cyanation sequence to furnish 7a–b

2-((1-Phenylbut-3-en-1-yl)oxy)decanenitrile (7a)

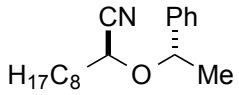




4:1 dr
$C_{20}H_{29}NO$
MW: 299.23

From **4a** (289 mg, 1.0 mmol) and 1-phenylbut-3-en-1-ol (162 µL, 1.05 mmol) following **GP6**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **7a** as a mixture of diastereomers in a 4:1 ratio*, as a colorless liquid (144 mg, 0.48 mmol, 48%). *Major diastereomer* - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 5.74 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.13 – 4.97 (m, 2H), 4.59 (dd, *J* = 7.3, 6.3 Hz, 1H), 3.89 (t, *J* = 6.5 Hz, 1H), 2.66 – 2.49 (m, 1H), 2.45 (dddt, *J* = 14.4, 7.4, 6.0, 1.3 Hz, 1H), 1.87 – 1.69 (m, 2H), 1.50 – 1.34 (m, 2H), 1.32 – 1.18 (m, 10H), 0.88 (app t, *J* = 6.8 Hz, 3H). *Minor diastereomer*§ - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.73 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.44 (dd, *J* = 7.3, 5.8 Hz, 1H), 4.14 (t, *J* = 6.5 Hz, 1H), 2.62 (dtt, *J* = 14.5, 7.3, 1.2 Hz, 1H), 2.47 (dddd, *J* = 14.2, 7.0, 4.1, 1.2 Hz, 1H), 1.87 – 1.73 (m, 2H), 1.47 (dd, *J* = 15.1, 7.1 Hz, 2H), 1.35 – 1.23 (m, 10H), 1.91 – 1.83 (m, 3H). *Major diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 133.8, 128.9, 128.6, 127.2, 118.8, 117.8, 81.4, 66.0, 42.1, 33.6, 31.9, 29.4, 29.3, 29.1, 24.0, 22.8, 14.2. *Minor diastereomer*§ - ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 133.9, 128.7, 128.5, 127.0, 118.8, 118.0, 83.0, 67.4, 41.8, 33.9, 31.9, 29.4, 29.3, 29.1, 24.8, 24.4, 22.8, 22.2, 14.2. IR (neat): 2923, 2854, 1088, 915, 756, 704 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{30}ON$ $[M+H]^+$: 300.2322; found: 300.2320. §Contaminated with an undetermined compound. *Determined by GC analysis on the crude residue.

2-(1-Phenylethoxy)decanenitrile (7b)

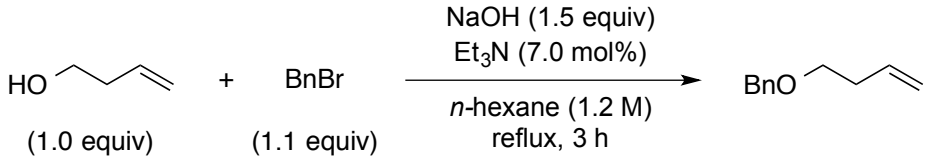


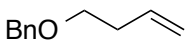
3:2 dr
$C_{18}H_{27}NO$
MW: 273.21

From **4a** (289 mg, 1.0 mmol) and 1-phenylethan-1-ol (127 µL, 1.05 mmol) following **GP6**. The crude residue was purified by FCC on silica gel (*n*-pentane/CH_2Cl_2 9:1) to afford **7b** as a mixture of diastereomers in a 3:2 ratio*, as a colorless liquid (224 mg, 0.82 mmol, 82%). *Major diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 4.72 (q, *J* = 6.4 Hz, 1H), 3.85 (t, *J* = 6.6 Hz, 1H), 1.87 – 1.68 (m, 2H), 1.50 (d, *J* = 6.5 Hz, 3H), 1.45 – 1.37 (m, 2H), 1.32 – 1.15 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H). *Minor diastereomer* - ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 4.65 (q, *J* = 6.4 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 1H), 1.90 – 1.75 (m, 2H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.34 – 1.18 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H). *Major diastereomer* - ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 129.0, 128.5, 126.7, 119.0, 77.8, 66.0, 33.7, 31.9, 29.4, 29.3, 29.1, 24.8, 24.0, 22.8, 14.2. *Minor diastereomer* - ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.7, 128.3, 126.5, 119.0, 78.4, 66.8, 33.9, 31.9, 29.5, 29.3, 29.2, 24.9, 22.8, 22.4, 14.2. IR (neat): 2925, 2855, 1455, 1090, 761, 699 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{28}ON$ $[M+H]^+$: 274.2165; found: 274.2173. *Determined by ^{1}H NMR analysis on the crude residue.

5. By-products

Synthesis of ((But-3-en-1-yloxy)methyl)benzene (6)



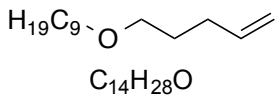


$C_{11}H_{14}O$
MW: 162.10

To a two-necks, 25 mL round-bottom flask equipped with a condenser was added 3-buten-1-ol (0.45 mL, 5.0 mmol, 1.0 equiv), triethylamine (0.05 mL, 0.35 mmol, 7.0 mol%), NaOH (300 mg, 7.5 mmol, 1.5 equiv) and *n*-hexane (3.5 mL, 1.4 M). The contents were stirred at 50 °C for 1 h. A solution of benzyl bromide, BnBr (0.65 mL, 5.5 mmol, 1.1 equiv) in *n*-hexane (0.7 mL) was added over ten minutes at this temperature. The reaction mixture was then heated under reflux for 3 h. After cooling to rt, the reaction mixture was quenched with water (5 mL), the organic phase was separated and the aqueous phase was back-extracted with Et_2O (2×3 mL). The collected organic phase was dried

over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by FCC on silica gel (*n*-hexane/EtOAc 9:1) to afford **6**[§] as a clear oil (539 mg, 3.32 mmol, 66%). Spectral data were in accordance with the literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 7H)[§], 5.85 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.19 – 4.99 (m, 2H), 4.57 (s, 1H)[§], 4.53 (s, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 2.39 (qt, *J* = 6.8, 1.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.4[§], 135.4, 128.6, 128.5, 127.9, 127.8, 127.7, 116.5, 73.1, 72.3[§], 69.8, 34.4. [§]Contaminated with BnBr.

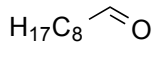
1-Pent-4-enoxynonane (SI-10)



$C_{14}H_{28}O$
MW: 212.21

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.10 – 4.93 (m, 2H), 3.43 – 3.37 (m, 4H), 2.16 – 2.08 (m, 2H), 1.71 – 1.52 (m, 2H), 1.57 – 1.52 (m, 2H), 1.27 (s, 12H), 0.88 (app t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 114.6, 71.0, 70.2, 31.9, 30.4, 29.8, 29.6, 29.5, 29.3, 29.0, 26.2, 22.7, 14.1. HRMS (ESI) calcd. for $C_{14}H_{28}O$ $[M]^+$: 212.2134; found: 212.2132.

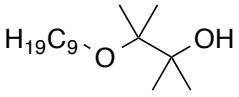
Nonanal (5aa)



$C_9H_{18}O$
MW: 142.14

Spectral and physical data were in accordance with commercially available nonanal [CAS = 124-19-6]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.8 Hz, 1H), 2.42 (tt, *J* = 7.3, 1.5 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.35 – 1.24 (m, 10H), 0.88 (app t, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 43.9, 31.9, 29.3, 29.2, 29.1, 22.6, 22.1, 14.1.

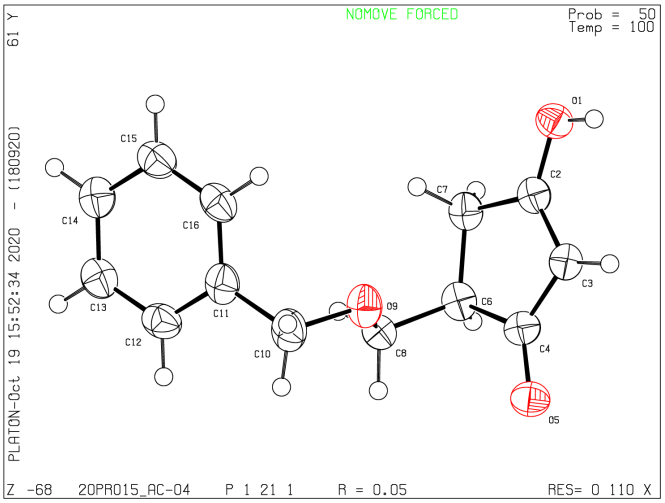
2,3-Dimethyl-3-nonoxy-butan-2-ol (5ab)



$C_{15}H_{32}O_2$
MW: 244.24

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, *J* = 6.3 Hz, 2H), 2.82 (s, 1H), 1.52 (p, *J* = 6.3 Hz, 2H), 1.35 – 1.26 (m, 12H), 1.18 (s, 6H), 1.13 (s, 6H), 0.88 (app t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.8, 75.1, 61.2, 31.9, 30.5, 29.6, 29.5, 29.3, 26.3, 24.4, 22.7, 19.5, 14.1. IR (neat): 2973, 2924, 2854, 1463, 1390, 1362, 1337, 1155, 1114, 1067, 943, 730 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{32}O_2Na$ $[M+Na]^+$: 267.2295; found: 267.2289.

6. X-Ray structure of 5-((benzyloxy)methyl)-3-hydroxy-cyclopent-2-en 1-one (3h)

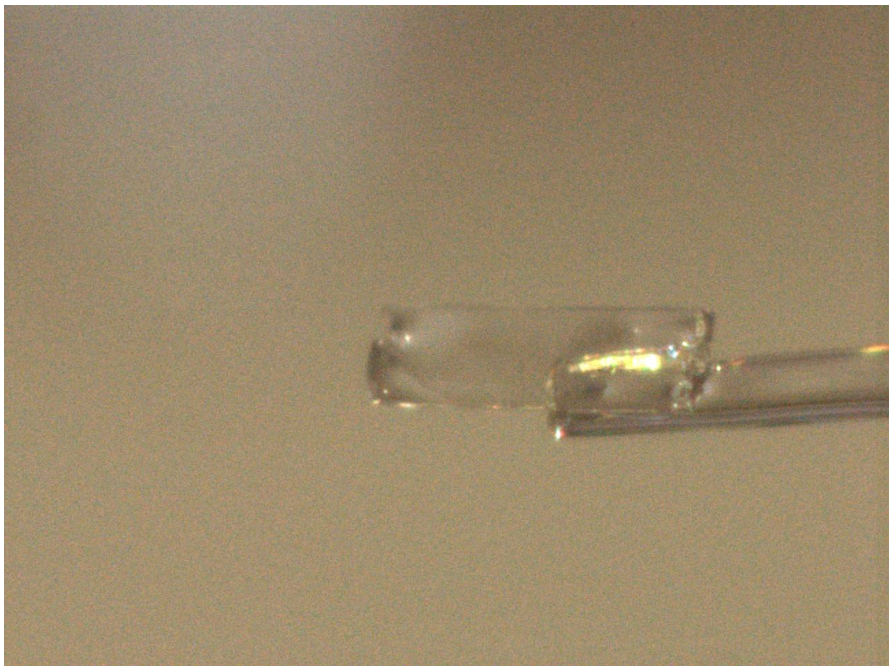


Crystal-Structure Determination. A crystal of $C_{13}H_{14}O_3$ immersed in parabar oil was mounted at ambient conditions and transferred into the stream of nitrogen (100 K). All measurements were made on a *RIGAKU Synergy S* area-detector diffractometer[1] using mirror optics monochromated Cu *K*α radiation (λ = 1.54184 Å). The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of reflections in the range 7.02° < 2θ < 155.478°. A total of 17946 frames were collected using ω scans, with 0.1 second exposure time (1s for high-angle reflections), a rotation angle of 0.5° per frame, a crystal-detector distance of 34.0 mm, at T = 100(2) K.

Data reduction was performed using the *CrysAlisPro*[1] program. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method using SCALE3 ABSPACK in *CrysAlisPro*[1] was applied. Data collection and refinement parameters are given in *Table 1*.

The structure was solved by intrinsic phasing using *SHELXT*[2], which revealed the positions of all non-hydrogen atoms of the title compound. All non-hydrogen atoms were refined anisotropically. H-atoms were assigned in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2Ueq of its parent atom (1.5Ueq for methyl groups).

Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. All calculations were performed using the *SHELXL-2014/7*[3] program in OLEX2.[4]



A single crystal of the compound mounted on a loop.

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Table 1. Crystal data and structure refinement for 20PR015_AC-04.

Identification code	20PR015_AC-04
Empirical formula	$C_{13}H_{14}O_3$
Formula weight	218.24
Temperature/K	100.01(10)

Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.36480(10)
b/Å	8.2341(2)
c/Å	12.6746(3)
α/°	90
β/°	96.549(2)
γ/°	90
Volume/Å^3	556.24(2)
Z	2
ρ_{calc}g/cm^3	1.303
μ/mm^{-1}	0.751
F(000)	232.0
Crystal size/mm^3	0.463 × 0.157 × 0.013
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.02 to 155.478
Index ranges	$-6 \leq h \leq 6$, $-8 \leq k \leq 10$, $-16 \leq l \leq 16$
Reflections collected	31933
Independent reflections	2218 [R_{int} = 0.1028, R_{sigma} = 0.0336]
Data/restraints/parameters	2218/1/146
Goodness-of-fit on F^2	1.110
Final R indexes [I>=2σ (I)]	R_1 = 0.0539, wR_2 = 0.1461
Final R indexes [all data]	R_1 = 0.0618, wR_2 = 0.1596
Largest diff. peak/hole / e Å^{-3}	0.35/-0.25
Flack parameter	-0.4(2)

Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 20PR015_AC-04. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O5	1331(5)	4761(4)	-440(2)	39.9(7)
O1	5677(5)	8771(4)	1704(2)	38.2(7)
O9	3051(5)	3577(4)	1977(2)	42.0(7)
C2	4103(6)	7652(5)	1304(3)	32.9(8)
C4	1989(7)	5739(5)	284(3)	33.9(9)
C3	3963(6)	6901(5)	342(3)	33.1(8)
C7	2198(7)	7063(5)	1982(3)	35.9(9)
C11	2789(8)	2091(5)	3627(3)	39.7(9)
C6	668(7)	5822(5)	1287(3)	35.1(9)
C14	2180(7)	2164(6)	5771(3)	41.7(10)
C8	537(7)	4172(5)	1786(3)	36.5(9)
C13	545(7)	1256(6)	5090(4)	42.1(10)
C10	3183(10)	2023(6)	2474(4)	47.8(11)
C16	4378(7)	2996(6)	4335(3)	41.8(10)
C15	4093(8)	3036(6)	5391(4)	43.9(10)
C12	842(8)	1226(6)	4022(4)	43.0(10)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 20PR015_AC-04. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	$\mathbf{U_{11}}$	$\mathbf{U_{22}}$	$\mathbf{U_{33}}$	$\mathbf{U_{23}}$	$\mathbf{U_{13}}$	$\mathbf{U_{12}}$
O5	35.1(13)	40.1(17)	44.1(15)	-4.0(13)	2.6(11)	0.2(12)
O1	39.0(14)	34.5(17)	41.4(14)	-3.5(12)	6.3(11)	0.3(12)
O9	46.4(16)	35.4(18)	45.7(15)	5.8(13)	11.9(11)	12.6(13)
C2	29.6(16)	31(2)	38.6(18)	3.0(16)	4.3(14)	6.6(15)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 20PR015_AC-04. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C4	29.5(16)	34(2)	37.3(18)	-2.2(17)	0.1(13)	6.6(15)
C3	26.7(15)	38(2)	35.5(17)	2.9(16)	6.0(13)	3.6(15)
C7	37.8(18)	32(2)	39.4(18)	1.5(16)	9.6(14)	7.2(16)
C11	48(2)	29(2)	43(2)	4.3(18)	9.0(16)	12.7(18)
C6	27.9(16)	35(2)	43(2)	3.4(17)	7.4(14)	7.4(15)
C14	37.0(19)	43(3)	46(2)	6.2(19)	6.1(15)	5.0(18)
C8	36.9(19)	33(2)	39.9(19)	0.8(17)	5.3(15)	-0.8(16)
C13	33.6(19)	41(3)	52(2)	6.2(19)	6.4(17)	1.1(17)
C10	68(3)	31(2)	45(2)	4.1(19)	10(2)	10(2)
C16	36.8(19)	32(2)	56(2)	5.5(19)	5.1(17)	0.6(18)
C15	41(2)	36(2)	54(2)	1.8(19)	0.2(17)	-1.3(18)
C12	43(2)	31(2)	53(2)	-1.1(19)	-3.2(18)	1.3(18)

Table 4. Bond Lengths for 20PR015_AC-04.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O5	C4	1.241(5)	C11	C10	1.501(6)
O1	C2	1.312(5)	C11	C16	1.384(6)
O9	C8	1.429(5)	C11	C12	1.403(6)
O9	C10	1.425(5)	C6	C8	1.503(6)
C2	C3	1.362(6)	C14	C13	1.379(6)
C2	C7	1.489(5)	C14	C15	1.383(6)
C4	C3	1.422(6)	C13	C12	1.381(6)
C4	C6	1.526(5)	C16	C15	1.364(6)
C7	C6	1.526(6)			

Table 5. Bond Angles for 20PR015_AC-04.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C10	O9	C8	112.4(3)	C12	C11	C10	121.4(4)
O1	C2	C3	129.2(3)	C4	C6	C7	103.9(3)
O1	C2	C7	117.3(3)	C8	C6	C4	111.0(3)
C3	C2	C7	113.4(4)	C8	C6	C7	114.2(3)
O5	C4	C3	128.4(4)	C13	C14	C15	120.5(4)
O5	C4	C6	121.7(4)	O9	C8	C6	107.0(3)
C3	C4	C6	109.9(3)	C14	C13	C12	119.1(4)
C2	C3	C4	108.4(3)	O9	C10	C11	113.1(4)
C2	C7	C6	104.1(3)	C15	C16	C11	121.3(4)
C16	C11	C10	120.5(4)	C16	C15	C14	120.0(4)
C16	C11	C12	118.1(4)	C13	C12	C11	120.9(4)

Table 6. Torsion Angles for 20PR015_AC-04.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O5	C4	C3	C2	-176.7(4)	C11	C16	C15	C14	-0.3(7)
O5	C4	C6	C7	175.5(4)	C6	C4	C3	C2	3.0(4)
O5	C4	C6	C8	52.3(5)	C14	C13	C12	C11	0.6(7)
O1	C2	C3	C4	178.2(4)	C8	O9	C10	C11	-74.2(5)
O1	C2	C7	C6	178.9(3)	C13	C14	C15	C16	-0.2(7)
C2	C7	C6	C4	3.7(4)	C10	O9	C8	C6	178.7(3)
C2	C7	C6	C8	124.8(3)	C10	C11	C16	C15	-178.1(4)
C4	C6	C8	O9	56.1(4)	C10	C11	C12	C13	177.9(4)
C3	C2	C7	C6	-2.2(4)	C16	C11	C10	O9	-59.7(6)
C3	C4	C6	C7	-4.2(4)	C16	C11	C12	C13	-1.1(6)
C3	C4	C6	C8	-127.5(4)	C15	C14	C13	C12	0.0(7)
C7	C2	C3	C4	-0.5(4)	C12	C11	C10	O9	121.3(5)

Table 6. Torsion Angles for 20PR015_AC-04.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C7	C6	C8	O9	-61.0(4)	C12	C11	C16	C15	0.9(6)

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 20PR015_AC-04.

Atom	*x*	*y*	*z*	U(eq)
H1	6632	9034	1251	57
H3	5006	7116	-199	40
H7A	1123	7967	2177	43
H7B	3015	6551	2639	43
H6	-1072	6247	1101	42
H14	1991	2192	6507	50
H8A	-218	4252	2462	44
H8B	-502	3431	1303	44
H13	-769	659	5352	50
H10A	4847	1538	2408	57
H10B	1895	1306	2096	57
H16	5694	3602	4082	50
H15	5209	3662	5865	53
H12	-289	611	3548	52

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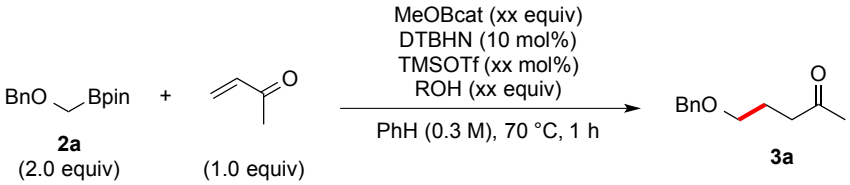
7. Optimizations of the radical deboronative conjugate addition of 2a to methyl vinyl ketone

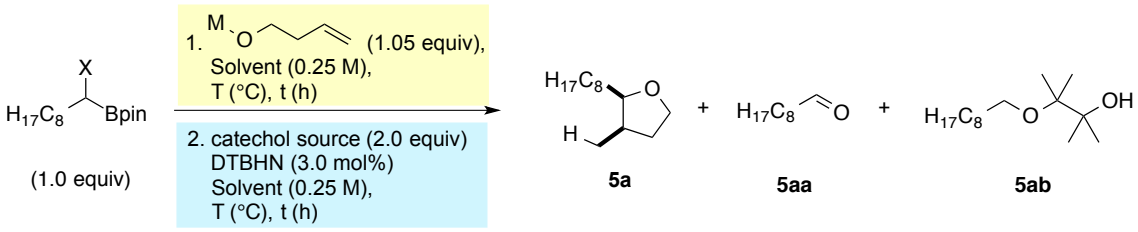


2a (2.0 equiv) (1.0 equiv) **3a**

Entry	MeOBcat (equiv)	ROH (equiv)	TMSOTf	yields
1	0.3	-	-	30%
2	1.0	-	-	43%
3	0.3	MeOH (0.1)	1.0 mol%	40%
4	0.3	MeOH (0.5)	1.0 mol%	54%
5	0.3	MeOH (1.0)	1.0 mol%	56%
6	0.3	MeOH (5.0)	1.0 mol%	57%
7	0.3	solvent	1.0 mol%	4%
8	0.3	MeOH (5.0)	-	59%
9	0.3	*t*-BuOH (5.0)	-	39%

Yield determined by ^{1}H NMR analysis

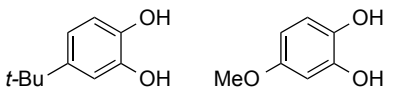
8. Optimizations of the radical deboronative cyclization to furnish 5a



Entry	Ionic process (Solvent, Temp., Time)	Radical process (Solvent, Temp., Time)	M	X	Catechol source	5a	5aA	5aB
1	PhH, rt, 16 h	PhH, 70 °C, 1 h	Li	Cl	TBC	42%[i]	24%[i]	15%[i]
2	PhH, rflx, 30 min	PhH, 70 °C, 1 h	Li	Cl	TBC	56%[i]	-	-
3	PhH, rflx, 45 min	PhH, 70 °C, 1 h	Li	Br	TBC	44%[i]	14%[i]	9%[i]
4	PhH, rflx, 1 h	PhH, 70 °C, 1 h	K	Cl	TBC	18%[i]	traces	56%[i]
5	PhH, rflx, 1 h	PhH, 70 °C, 1 h	Na	Cl	TBC	22%[i]	-	57%[i]
6	THF, rflx, 1 h	THF, rflx, 16 h	Li	Cl	TBC	29%[ii]	-	9%[ii]
7	TBME, rflx, 16 h	TBME, rflx, 1 h	Li	Cl	TBC	23%[ii]	-	2%[ii]
8	THF, rflx, 1 h	PhH, 70 °C, 1 h	Li	Cl	TBC	69%[i]	-	7%[i]
9	THF, rflx, 1 h	THF, rflx, 3 h	Li	Cl	4-MeOcat	45%[ii]	-	4%[ii]
10	THF, rflx, 1 h	PhH, 70 °C, 45 min	Li	Cl	4-MeOcat	60%[ii]	-	5%[ii]

[i]Yield of isolated product. [ii]Yield determined by quantitative GC analysis.

Catechol sources:



TBC 4-methoxycatechol

Declaration of consent

on the basis of Article 18 of the PromR Phil.-nat. 19

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